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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	Meditab Specialties Pvt Ltd, 352, Kundaim Industrial Estate Kundaim, Goa 403 115, INDIA
Corporate address of manufacturer	Meditab Specialties Pvt Ltd.: Corporate C1-Pooja Apartment, 17, Hariyali Estate, Vikhroli (West), Mumbai-400083 Telephone:+91 22 2571 8600/ Facsimile: +91 22 2578 3204 Corporate Identity Number : U23240MH1996PTC104442 Cipla Ltd: Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai – 400 013 Phone : +91 22 24826000 / Fax : +91 22 24826120 Corporate Identity Number : L24239MH1935PLC002380
Inspected site	
Manufacturing license number, (delete if not applicable)	366 and 391
Inspection details	
Dates of inspection	20, 21, 22, 23 June 2016
Type of inspection	Routine
Introduction	
Brief summary of the manufacturing activities	The site was active in the manufacture, packaging, testing and storage of finished pharmaceutical products.
General information about the company and site	Meditab Goa was located 25 km from Panjim, the capital city of Goa. There were approximately 200 employees. There was a production capacity of 50 million tablets per month according to the opening meeting presentation. Wet, dry or direct compression methods were used. The facility was regularly updated. There were two FBDs, one roller compactor with a capacity of 100 kg/hr, and two compression machines only. There were 10 HPLCs operated using Chromeleon in Quality Control. LIMS was under implementation. Cipla Corporate Quality assurance governed the site's quality policy and Cipla performed technical transfers, training, was responsible for SOPs and updates.

	Significant changes since last WHO inspection: - SAP software implementation in 2014. - New automated PLC-controlled compression machine installed in 2016. - New screw type air compressor (friction free design) was installed in 2015.
History	The facility was started in 1998 and had approval from the Food and Drugs Administration of Goa for carrying out manufacturing activities, which was valid until December 2016. The last WHO inspection was in November 2013, and the site was also WHO inspected in February 2011 and January 2009. It was last inspected by CDSCO 8 and FDA-Goa in May 2016. They have never been inspected by the US FDA or by EMA. *They were inspected by the Ministry of Health in Ukraine.*
Brief report of inspection activities undertaken	**Scope and limitations**
Areas inspected	The inspection focused on general principles of GMP and the production and control of the above-mentioned WHO prequalified products and products under assessment. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.
Restrictions	n/a
Out of scope	The basement manufacturing area allocated to herbal products was not inspected in detail since this was not a product for WHO PQ.
WHO product numbers covered by the inspection	• NT003 Praziquantel tablets 600 mg • HA352 Efavirenz tablets, film-coated 300 mg • HA353 Lamivudine tablets 150mg • HA039 Nevirapine tablets 200mg • HA365 Lamivudine, Zidovudine and Nevirapine tablets 150/300/200mg • HA060 Lamivudine/Zidovudine Tablet, Film-coated 150mg/300mg

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis

FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
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

Product quality review (PQR)

PQRs were conducted annually according to the applicable SOP (17/Feb/2016). The content of the current SOP was found in compliance with WHO PQR requirements. The following number of batches of WHO prequalified products were produced in 2014, 2015 and 2016:

	2014	2015	2016 (to date)
NT003 Praziquantel 600mg	0	17	06
HA353 Lamivudine 150mg	5	3	4
HA352 Efavirenz 600 mg	0	0	0
HA039 Nevirapine 200mg	8	1	0
HA365 Duovir-N	141	25	1
HA060 Duovir	0	0	0

PQR Example:
The last report for Duovir-N (Lamivudine 150 / Zidovudine 300 / Nevirapine 200) tablets was done for the period from May 2015 until April 2016. The report was finished on 16 June 2016. The final statement gave the information that the manufacturing, testing and packing process and parameters are within the specification with respect to quality, yield and stability.

There was a total of 11 batches manufactured during the review period. No batch was rejected.
Relevant QC results were trended. Information about the qualification of critical equipment and utilities used was summarized in detail. Information about purified water, compressed air, humidity and water monitoring was part of the evaluation. Specifications were fulfilled. No OOS results were observed.

Review of process, analytical and microbiological validation was done. There were no changes which would require revalidation.

Description of all changes relevant for the product, including the reason for the change was part of the PQR.

Quality risk management (QRM)

Quality risk management had been implemented through SOP CQA-246-09 (02/March/2015).
The procedure followed a 'Failure Mode, Effects and Criticality Analysis' (FMECA) model. Risk priority numbers were required to be determined whereby severity, occurrence and detection were used to identify the levels of existing controls and identify gaps to mitigate potential risks. In general, the procedure was found adequate except that some of the terminologies (such as definition of serious and hazardous) were not defined. This was also an observation from last inspection.
New version of this SOP including the missing definitions was issued on 31/May/2016 and will be effective after training from 29/June/2016.

Scales of 1 to 5 were used for severity, occurrence and detection. An RPN up to 25 was classified as minor and 76 to lesser than 125 was classified as critical.
For RPN rating > 25, an action plan was required.
A log and annual schedule of risk assessments was maintained.

Examples:
Risk assessment for RMG (Rapid Mixer Granulator 630 L): Risk Management team was led by the Department Head. Complete risk evaluation was documented and after effective implementation of the action plan the assessment was finalized on 16/Feb/2016.

Risk assessment for the Fluid bed equipment 125 / 500 L was done in 2013.
During wet granulation process, which includes rapid mixer granulator step before the fluid bed drying process, manual raking process would be necessary, including opening the FBD bowl and manual mixing / loosening the sticking granules from the wall of the equipment and crushing of lumps. This process requires adequate control from the viewpoint of personnel and environmental hygiene together with adequate processing by the personnel at the area. However, description of the process and the control measures was missed in the risk assessment document.
Evaluation was finished after implementation of additional control measures specified in the action plan. Review showed reduction in RPN number due to improvement in detection level. Re-evaluation was planned for September 2016.

Some areas where the required risk assessments were not documented, were identified during the inspection and this was resolved in the CAPAs.

Change Control System

The SOP for "Change Request" (06/Nov/2015) was available and was reviewed. A flow chart was included as annex A1. Documentation was done with the CipDox software. Change coordinator from QA department was in charge to verify and monitor the activities together with change control.
Document history was documented together with the change of the procedure (document review sheet, archived with the valid documents in the CipDox document management system).
The Change Control log were available and checked for 2015 and 2016.

Examples:
Change F/F/MT/15/05/001: New screw type air compressor, capacity 300 cubic feet per minute, was installed in 2015. Risk analysis and qualification documentation was available.

For details on compressed air system, refer to section 12.

Supplier qualification
The SOP on Selection, evaluation, and approval of manufacturer (01/April/2015) was available. A risk matrix for excipients was in place. Decisions about the need of audits were made based on the type of material (functionality), the quantity in the product and the route of administration.
Primary evaluation was done based on analysis of samples and questionnaire. Need of additional documents for API manufacturers (e.g. GMP, TSE/BSE certificates) was defined.

Audits should have been done every 3 years. Requirements for the auditors were defined.

Manufacturer for Magnesium stearate: Mallinckrodt Inc., St. Louis, U.S.A. (Name of the company was changed to Covidien), no report for the site audit was available. (Report from 16/July/2013 shown was for other sites and other excipients).
The last audit from the manufacturing site was documented on 23/Feb/2009. The audit report was only 4 pages. Information about raw material used was missing.

Nevirapine was supplied by Shanghai Desano, Binhai Road and was audited on 18-19 January 2016. Closeout for this audit was done on 30 March 2016 after evaluation of all CAPA's.

Deviations

Deviation Handling Cipla Corporate SOP dated 30-October 2015, version 2.0, were reviewed. The deviations logbook for 2016 was reviewed as well. There were approximately 5 deviations per month. An example was reviewed for acyclovir 400 mg dispersible tablets, where the weight of sized granules was more than the theoretical weight mentioned in the batch records. The LOD of the dry mixed material was on the lower side compared to the dried granules. It absorbed water during processing which led to the higher weight. The CAPA was to monitor the trend of five batches and the yield limit was updated based on this after filing a change control. This was considered acceptable.

Corrective and preventive action (CAPA)

Logbooks of corrective and preventive actions were presented for 2016 and 2015. This included CAPA No., date, reference documents, description of non-conformity and corrective action, responsible department, logged by, CA target completion date, PA target completion date, CAPA close out date, closed by, CAPAER due on, Close out for CAPAER and "closed by", as well as "remarks". The logbooks were generally found satisfactory.

Out of specifications (OOS)

In 2015, there were approximately 36 OOSs in total. There were 10 OOS in total for assay during that year. There were several different types of logbooks that covered anomalies in the laboratory:
-OOS logbooks
-Log of analytical incidences
-Log for system suitability failut/software error (finished in March 2015)
-Log for out of trend in the QC laboratory
-Log for pre-evaluation incidence (tihs is equivalent system suitability but is only for resolution between 2 peaks and theoretical plates)
The analytical incidence investigation report and full analytical report for praziquantel tablets USP 600 mg for WHO, was reviewed. It was stamped as passing and was verified by Lab QA as of 15.06.2016 for batch KT4231, Container of 100's, 24 months, 30^{o}C/75%RH. .
The list of function and malfunction details of chromatographic analysis using chromelon software for FMECA, was reviewed.

The CAPA report from the last WHO inspection was reviewed and was found acceptable.

2. Good manufacturing practices for pharmaceutical products

The infrastructure of the facilities, the manufacturing and quality control procedures were adequate and executed by adequately qualified personnel. GMP standards were adhered to an appropriate level.
Minor observations nevertheless require attention to further improve the level of GMP compliance.

3. Sanitation and hygiene

A high level of sanitation and hygiene was observed in all relevant areas during the inspection.
This was supported by the suitable design of the manufacturing environment and equipment, as well as the effective HVAC system.

4. Qualification and validation

Validation Master Plan

A version from 31/Dec/2015 was reviewed. Details of the current qualification and validation programme (annual schedules) were part of the document. However, a complete overview about the state of qualification, process validation, cleaning validation and analytical method validation was missing. This was resolved in CAPAs.

Cleaning validation

The cleaning validation protocol was part of the current SOP (15/Jun/2016). Validation of analytical methods was required for measurement of product in the rinses, measurement of product in the swabs and measurement of cleaning agent in the rinses/swabs (if applicable). The efficiency of sampling recovery of API by the analytical method should be assessed.
About 100 mL aliquot per active ingredient from the final rinse for measurement of active ingredient and about 50 ml aliquot from final rinse for measurement of cleaning agent as per SOP should be withdrawn for the rinse analysis. Swab sampling should be done according to the individual sampling plans.
Additionally, equipment and its parts should be visually inspected to ensure that it was clean.
Microbial verification was included.
Establishment of worst case product should be done on basis of solubility, least therapeutic dose (potency) and toxicity (least PDE value).
Selection of next product for calculation of acceptance criteria should be done based on the maximum daily dose of the product and minimum batch size.
Acceptance criteria (MAC = maximum allowable carryover) should be calculated by Dose criteria, 10 ppm criteria and PDE criterion.
Cleaning validation matrix and establishment of worst case product was documented adequately according to company CAPAs.

A new concept of consideration of PDE (permitted daily exposure) in the calculation of the MAC was implemented in June 2016. A new calculation of MAC limits was started.

A document for "Establishment of worst case product and calculation of acceptance criteria" (18/Oct/2012) was available. According to this document, worst case products were: Efavirenz and Alprazolam tablets. But validation documents for this products were not available. Explanation was given that products were not produced as planned. However, documentation for selection of other worst case products was not available.

The validation report from 30/Jan/2013 was available. Mebendazole tablets 500 mg were chosen as the worst case product. MAC values were calculated for the product aciclovir tablets (batch size 45 kG / 150000 tablets). Results of all analyses were found below the detection limit (0.25 µg per swab). The limit of detection was not taken into account during calculation of the results for rinse samples. Recovery factors for swab and rinse samples were not given in the report. Other errors were identified during the review of the report which were corrected in the company CAPAs.

In 2016 ,recalculation was done after implementation of the new PDE criteria. PDE criteria was found most stringent for the worst case product Mebendazole tablets 500 mg. All results obtained during cleaning validation found well within the new limits, hence existing cleaning validation stands valid. Issues raised were resolved in the company CAPAs.

Process validation and technology transfer

This was reviewed for Duovir N Lamivudine, Zidovudine and Nevirapine tablets. The protocol dated from 8 May 2013. The process was initially transferred by Cipla to Meditab in 2009 and included the manufacturing of 3 batches of 624.00kg at each site (Cipla Goa Unit III and Meditab), but was revalidated by Meditab, on 3 commercial batches in 2013 of the same size.

For Praziquantel, the product transfer report was also reviewed. It dated from May 2014. It was done on the 95.0 kg batch size (100,000 units). This was considered acceptable.

5. Complaints

The logbooks for market complaints were reviewed. They were registered starting in in 04.2014 and in April 2016. There were no complaints for WHO products and only a small number of complaints for non PQ products. One example was a print error of expiry date on carton. It was judged non critical. It had been reported by Karen Johnson of Cipla and was found for Cipalat retard tablets.

The procedure for complaints version 2.0 from Cipla Corporate, was reviewed. This SOP was thorough and included investigation of suspected counterfeits. It also included internal complaints.

6. Product recalls

The recall procedure version 2.0 dated 21-Aug-2015 from Cipla Corporate) was reviewed. It was considered satisfactory and described appropriate timelines and the parties to be informed, as well as recall validation. The responsibility of conducting a recall was Cipla Corporate's since they were responsible for the distribution of the product – this was documented in the Annexure to the SOP, entitled "Flow chart of recall process for export market when contract giver is MA holder".

The last mock recall report was completed on 1 October 2014 and was done using the Cipla Bangalore unit (not Meditab) for a batch of product in transit, simulating a moldy odor in the PVC/PVDC film during packing for a product. The dummy recall was initiated on 29.09.2014. The report concluded that the recall was effective and done within the timelines specified in SOP CQA 32. It was seen to have taken approximately 72 hours.

The last real recall was from Cipla and was dated 08.07.2015 for ibuprofen children suspension for export from Cipla Kurkumbh, due to breaking off of the bottle neck when opening the bottle of children's ibuprofen suspension. This was due to a lot of defective PET bottles from Trimuthi Polymers. Out of 2749 units dispatched, only 49 were recalled back from the market since it was already distributed to pharmacies. This issue was communicated to TGA as the product was distributed in Australia. It was closed on 29.03.2016.

7. Contract production, analysis and other activities

The company did not outsource any of their finished dosage form production. Only atomic adsorption spectroscopy (for magnesium stearate) was outsourced to Sitec in Mumbai (FDA approved according to the company). Three other laboratories were also part of the agreed sub-contractors for analytical testing, namely Bee Pharmo Labs, MJ Lab Private Ltd and Geo-Chem Laboratories (Rajkot) Pvt. Ltd, Cipla Goa, Analytical Solutions (Mumbai), Choksi Laboratories (Vapi), Okasa Pharma (Satara) and Choksi Laboratories (Indore). It said that prior to sending the samples for analysis at above listed contract labs, approval from local authority (FDA) is required. There was no requirement for verification of compliance for other regulatory authorities.

The technical agreement between Cipla and Meditab was dated 19.09.2014 and was signed off by Mr. Savio Dourado from Head Global Quality Operations of Cipla and by Unit Quality Assurance Heads of the 3 Meditab Sites (Satara, Agarwal (Daman) and Kundaim (Goa)). All of the responsibilities were adequately distributed between the contract giver and contract acceptor.

Sourcing of materials (active, excipients and packaging) was done by Cipla including qualification of suppliers. Stability (initial and on-going) was the responsibility of Meditab. The main responsibility for recalls and complaints was with CIPLA. PQR was the responsibility of Meditab.

Transportation / Shipping of finished products up to the depot (Central Warehouse from CIPLA, operated in Mumbai) was in the responsibility of Meditab.
The quality agreement with the shipping agency (Sunit Transport) was signed in March 2015.
Point 13 of the agreement contained the statement: "Where special storage conditions (…) are required during transportation, these should be provided, checked, monitored and recorded".
However, there was no provision of special storage condition. It was fixed that the transport should be done with closed and covered vehicles. This issue was resolved in CAPAs.

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

The Self-Inspection SOP dated 28 April 2016 from Cipla Corporate was reviewed. The last self-inspection by Meditab was done on 04.05.2016 and on 05.05.2016 for packing and was closed on 16.06.2016. The last self-inspection for QA was done on 03.06.2016-04.06.2016. The self-inspections for other departments were pending. These were repeated every 6 months. The quality assurance self-inspection was not yet closed.
The persons who performed the self -inspection of the packing department included a senior employee who was section head in QA (Quality Operations) and a Team leader from QA as well as the section head of the coating section in production. The staff that was contacted during the self-inspection were two production officers in Packing and an export coordinator. According to the SOP, the inspection team should include an inspector from quality assurance and inspectors should be independent from those having direct responsibility for the areas being inspected. This was seen to be implemented.

The list of certified inspectors of Meditab, Goa, was reviewed and included 22 employees.

A corporate self-inspection by Cipla was performed from 11.04.2016 to 14.04.2016 was also reviewed. It was not yet closed out due to pending CAPAs.

Arrangements for self-inspection were acceptable overall.

9. Personnel

In general, the personnel met during the audit were experienced, knowledgeable and appeared competent. Adequate numbers of personnel were present to ensure completion of all necessary tasks. Job descriptions were reviewed for a few selected members of personnel. They were considered acceptable and sufficiently detailed and up to date.

10. Training

The Current Training SOP was valid from 20/Nov/2015. According to the SOP, training matrixes should be done for the identification of training needs and the documentation of the competency of each person.
Induction, job specific and on-going training, training of contract / temporary workman and auditors as well as evaluation of trainings through tests was part of the SOP.

Examples of the personnel training were checked together with the update of the change control procedure in Nov/2015. Training was done on 03/Nov/2015. It was found, that there were some differences in between the training and competency matrix and the participants at the training on the new SOP.
Example: Mr. Sourav Das and Mr. Pradeep Patil from production (granulation officers) as well as Mr. Rahul Pandhare and Mr. Javed Nasardi did not join the training session about the valid SOP but were given as competent in the matrix.

Completeness of training for the new SOP on change control was not documented.
It was explained by Meditab, that only workers which should work with the new CipDox change control system, were included in the training. But from the viewpoint of the inspectors, training was necessary for everyone which should be competent for the new change control SOP.
Also current training and competency matrices were done in 2016 after the implementation of the new change control system and should only give competence to the people which are trained on all current SOP's.
Whole system of identification of training needs should be revised. Clear connection in between topic numbers used in the training matrices and relevant SOP's should be available.

11. Personal hygiene

Arrangements for personnel hygiene were generally found suitable. No non-compliance was observed during the detailed tour through the production and warehouse area.
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.

Handling of gloves used in production

During the production tour it was observed that gloves were used for primary processing. However, together with this, gloves came also in contact with the open product. For instance, they were used to bring product residuals sticking on containers back to the product batch.
The SOP Handling of hand gloves (10/March/2016) was reviewed.
Sampling and approval of supplied gloves was done by QC. According to the department procedure (MT-150, 21/Oct/2014) gloves were changed during every break.
Also some precautions for the correct usage of gloves were part of the SOP (e.g. product should not be handled with torn gloves). Some additional measures were defined in the SOP about dispensing of raw material.
Material specification for gloves used during primary production was available (Blue Nitrile Powder Free).

12. Premises

There was only one manufacturing building on site. It had three floors. On the lower floor, there was a small production area dedicated to herbal medicinal products, packing material stores and receipt of packing materials.
The main production area, raw material storage and material entry together with sampling and dispensing areas were situated at the ground floor.
The first floor was used for change rooms, quality control (including microbiological laboratory) and service floor (installation of HVAC system, dust extraction system).

The flooring in the production and storage areas were tiled with kotah stone and in critical areas such as microbiology laboratory, raw material sampling, sifting and dispensing cubicles were epoxy coated.
No activity other than manufacturing of pharmaceutical formulations was carried out at the site.

Raw material receiving areas and warehouses

Areas for goods receipt, initial cleaning using a vacuum cleaner and quarantine/finished goods were situated at the ground floor. The goods unloading dock was accessed from the warehouse via an airlock. A common sampling room fitted with LAF cabinet equipped with HEPA filters was used for both active and excipients whereas a separate sampling room was available for sampling of packing materials.
The storage facilities allowed for effective segregation and security of materials and products at different stages of processing and those rejected. The materials were stored in mobile rack system with appropriate segregation.
All areas were in a good state of cleanliness and maintenance.
Access restrictions, measures of pest control and monitoring were found appropriate.

Packaging materials warehouse

The packaging materials were housed on the lower ground floor. All areas were found clean and tidy. Temperature and relative humidity (RH) in the warehouse were monitored.
The quality control laboratory for packaging material was situated next to the packaging material warehouse.

Dispensing Rooms

There were two dispensing rooms, one for active materials and one for excipients, each fitted with a with a LAF cabinet equipped with HEPA filters. Entrance to the dispensing room was through change rooms where appropriate gowning took place. The materials were transferred through pass boxes.
The dispensing operations were performed using new ERP System (SAP).
SOP for Dispensing of raw materials (29/March/2016) was available and checked in detail. Dispensing was done by personnel from stores. Production personnel was there for doing the double checking of the weighing procedure and the documentation.
Detailed description of the dispensing process, including planning, preparatory work, area cleanliness environmental checks (Temperature, humidity, differential pressure), personnel hygiene (wearing of snood, nose mask, shoe covers, gloves over gown), weighing, labelling and documentation was done. Documentation at the current stage was done on manual way including double check be a second operator from production.
Future plans for the implementation of the weighing results / records in the BMR did exist.

Production areas

All manufacturing operations for WHO products were carried out in ground floor.
Materials from dispensing area were transferred via airlock to dispensed material storage area inside production.
Production area was found well designed and maintained.
Entry into the premises had to be done in two steps through well designed change rooms.
Photographic illustration and SOP's for the entrance procedure was in place.

Details of production and packing area:
The big production room for granulation was equipped with rapid mixer granulator (630 L, Bowman Archer) and fluid bed equipment (500 L). Additional equipment for smaller batch size was available.
Further cubicles in use:
- 1 cubicle for sifting (vibratory sifters),
- 2 cubicles for blending (octagonal blenders),
- 5 cubicles for compression (well equipped with compression machine, dedusters, online metal detectors),

- 2 cubicles for coating (NEOCOTA 50D, Autocoater 350 L),
- 1 inspection room (final inspection of appearance)
- 1 cubicle for packing of bottles (equipped with an unscrambler with a cleaning machine, silica gel inserter, tablet counting machine, cotton inserter and inline capping machine together with IPQC equipment for tablet counting and torque control),
- 3 cubicles with blister packing machines,
- IPQC laboratory (e.g. with halogen moisture analyzer, tapped density apparatus, hardness tester, disintegration test apparatus, friability tester),
- in-process store / clean equipment room,
- finished bulk store
- Packing Hall with secondary/tertiary packing lines.

Test weights for daily testing of scales used in production and sieve inspection boards were available.
Packing lines were well equipped with systems for automatic control (camera control, weight checker).
Compression tools were stored at appropriate condition (separate lockers for every punch set, punch stock card, punch set destruction records). Rotation of punches and dies was done and documented in an appropriate way.
Synthetic lubricant (SENTINEL) was used (QC approval was labelled) for preparation of tools.

An additional area for production was placed at the lower ground floor. This area was only used for one herbal medicinal product (calcium sennosides tablets). This was to prevent contamination of the main production area with herbal products.
This additional production area was built according to the same GMP design as the main production area at the ground floor. Area was equipped with cubicles for granulation, blending, compression, primary and secondary packing as well as IPQC laboratory, washing area and in process store.
Pressure differences in between the different cubicles and the corridor as well with regard to airlock and adjacent store for secondary packing material were monitored by MAGNEHELIC's and found within the defined range.

Water purification system
The potable water supply was from the local industrial development corporation. Potable water after pre-treatment was used as in feed water for Purified water system which consisted of RO + EDI modules and UV units.
Purified water of required quality was obtained and analysed chemically and microbiologically every week to meet specifications.
Continuous on line monitoring of pH, conductivity, pressure and flow rate was in place. There was an off-line TOC provided in the chemical laboratory.
Water was stored in a steam jacketed stainless steel storage tank fitted with a 0.45 micron hydrophobic vent filter.
Stainless steel loop with 10 points of use was installed for appropriate water supply to production.

AHUs
The environmental conditions were assured by air handling units supplying all the facilities in the primary production (controlled) areas. The controlled areas were qualified as Class "D" (ISO 8). The AHU's were qualified, regularly maintained and monitored.
38 AHU's were installed on site.
Differential air pressure was set up between areas of different air classification to prevent cross contamination. The process area corridors were maintained at a higher pressure with respect to the adjacent manufacturing

rooms. A pressure cascade of 15 Pascal was maintained to ensure that direction of airflow is from clean corridor to the cubicle and from classified areas to non-classified areas.
Log books for documentation of pressure differences were implemented.
Special attention was also paid to the design of the packaging lines. Primary packing area was held under overpressure with regards to secondary packaging. MAGNEHELIC's were installed beside the wall breakthroughs to monitor the pressure difference in between primary and secondary packaging.
AHU-44, dedicated for the granulation area, was chosen for detailed evaluation.
Qualification documents including detailed drawing for the AHU were available.
Differential pressure at the filter was checked online for the HEPA filter's. Pre and intermediate filters were cleaned every week and visual checked for integrity after cleaning and reusing.
HEPA filters were installed in the AHU. From there, cleaned air was supplied through air diffusers to the relevant area.
Return air dampers and supply air dampers were regulated manually. In addition, automatic fire dampers were installed to reduce the airflow in the system after switch-off.
HEPA filter integrity was checked together with air velocity, air changes per hour, leakage checks for the duct system, pressure differentials, air flow patterns, and particle count at rest conditions every year. Last report for AHU-44 was done on 3 June 2016.
Limits for particle monitoring were established in accordance to grade D (ISO 8).
All results were found in accordance to the limits.
In addition, in operation studies and recovery tests were done.
Alarm limits were not fixed until now. Results were found far below ISO 8 condition (e.g. 123675 Particles > 0.5 µm/m^3).
Installation of AHU's in the technical area was seen and found in good state. However, dust extraction system was found connected with the AHU's of relevant areas. According to the drawings seen, exhaust air from dust collectors was filtered through 1 µm cartridge filters of the dust collectors and afterwards was passed to the AHU's and mixed into the return air from production area. This connection was not shown in the drawings of the relevant AHU's. Documentation with regard to risk assessment (possibility of cross contamination caused by contaminated air from dust extraction system / filter breakthroughs) was not available.

Compressed Air

Compressed air was generated in-house and used for various manufacturing operations. According to the description in the SMF oil free compressor is used for the generation of compressed air. Compressed air is supplied to a receiver, then passed through refrigerant type air drier for removing moisture content and filtered through a set of filters of porosity of 5 µ, 1 µ and 0.01 µ before supplying for usage.
There were two compressors (Ingersoll Rand) each of 300 CFM were available for use.
Installation of the two air driers was done in 2013. The handover certificate of equipment was signed on 14 August 2013 and was reviewed.
Together with the correct function of the air dryer, it was argued, that there is a monitoring and recording of the dew point of 5°C which would make sure the correct function. However, according to the drawing the temperature probe was installed at the refrigerant circuit, not measuring the water content into the compressed air line.
1 µm pre-filter and 0.01 µm filter for compressed air (Domnick hunter, filter elements 025AO and 025AA) were installed at the service floor for every relevant point of use.
Complete drawing of the system was available.
Clear description of the usage and information about specification, monitoring and distribution system was missed in the SMF.

Testing done in October 2015 showed that all results were within the limits. Testing was done according to the specification, including parameters of the EP monograph for breathing air (e.g. carbon dioxide, water and oxygen content). In addition, particle content (NMT 100 particles / m3 of 5 µm and above + NMT 3520 particles / m3 of 0,5 µm and above) and microbiological quality (limit 5 cfu/ 1000 L) was monitored. Test procedure, including sampling procedure (1035-MM-015-INH, 12/Feb/2016) was used.
Limit for water content was given with NMT 10 ppm. All results were documented with 2 ppm. GASTEC detector tubes were available, showing range from 1 – 18 mg/l. It was explained by Meditab that the normal reading was 2 mg/l and this should be the same as 2 ppm. Calculation was checked in detail and found incorrect. 2 mg/l are equivalent to around 2700 ppm moisture content of water (20°C, 1013 hPa).
This water content needs complete evaluation with regard of the risk for processes and products. Possibility of higher pressure in the compression and drying stage (could also reduce the water load of the air) and addition of an adsorption dryer should be checked for better control and reduction of the water content. In addition, continuous water monitoring 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.
A risk assessment procedure and design verification for the whole compressed air system was necessary.

13. Equipment

Adequate numbers of equipment for production and in process testing with regard to the products manufactured at the site were available. Good design and cleaning status was found. Calibration, qualification (providing information about qualification, requalification and next required requalification) and status labels (clean, in use, current product) were fixed at the equipment.
For further details, refer to the section 12 above.

Cleaning procedures

Cleaning procedure for Rapid mixer granulator was seen (13/Feb/2013).
Dismantling and assembling was part of the procedure.
As general cleaning agent, 0.1% Teepol solution was used.
Assembling of the machine will be done after line clearance tests direct before the start of new production. Line clearance checklist for the documentation of these checks was available and will be part of the BMR.

14. Materials

SOP's Dispensing of packing material (27/Jan/2016) and Transfer of material from one stage to another (21/April/2016) were seen.
Dispensing and transfer process was described in detail.
According to the SOP's all packing material should be covered with polybag before transfer to packing. The same should be done during the transfer of excess packing material to stores department.
SOP Receipt of materials (CQA/S-17, 14/Jan/2015):
Foils and films should be deboxed at material receipt unloading bay / airlock
However, additional care should be taken to the correct primary packing of primary packing materials. Plastic bags should be used and integrity of this should be checked after deboxing.
Two cases of primary blister materials in defective plastic foil were found during the tour through production and storage area.

A Goods Receipt (GR) was created in SAP and a unique SAP batch no. was generated for the purpose of identification and traceability and then the GR was automatically transmitted to QC to initiate sampling activity.

A unique A.R. number is assigned against the SAP batch number. Sampling was done by QC personnel. After analysis, materials were passed or rejected and labelled appropriately.
Information about approved suppliers was included in the material management system.
Several examples for materials (Nevirapine, Lamivudine, Zidovudine, Praziquantel) were checked and the materials found in good condition and from approved supplier.
For further details, refer to the section 2.12.

Rejected materials and products
Rejected materials and products were stored separately in rooms for rejected raw materials and rejected finished products. Quality Assurance decided on the action to be taken. Records were maintained.
200 kg Ciprofloxacin were seen to have been rejected because of an impurity problems.

15. Documentation

Document control
As noted in the report from the previous inspection, documents were still being controlled according a Cipla corporate document control policy. This area was considered acceptable overall.

Batch registers
Information about batch release was kept in the SAP system. Information was verified. The BMR for detailed follow up was selected for review.

Master formulae, Batch manufacturing and packaging records
Complete record for Duovir-N tablets (Lamivudine 150 / Zidovudine 300 / Nevirapine 200), batch KG60222, was verified in detail.

The bulk was produced under Batch number KG60185. The master manufacturing formula was available (Bulk finished good code 31002311, Version no. 01, 12/Aug/2014). Batch size was 600000 (624 Kg, 1060 mg per tablet, 1040 mg per uncoated tablet).
In the master formula it was determined, that the quantity of the API's should be adjusted if the assay of the API was below 99,50 %.
Dispensing was documented in the manufacturing work order (starting on 26/April/2016).
Further steps were documented in the BMR (BMR was released based on the Master BMR on 21/April/2016; Master BMR was used since 06/Nov/2014).

Granulation was done with FBD 500 L on 28-29 April2016 (lots A until D).
Final step, inspection of coated tablets, was done on 04 May 2016. 1.3 Kg of tablets were rejected (0.21%).

Packing was documented in the BPR and started on 10 May 2016.
The checklist for line clearance was available.
Secondary packing was finished on 13 May 2015.
Reserve samples (6 containers a 60 tablets) and stability samples for ongoing stability testing (19 containers) were taken.

Batch release
Batch release was done based on the applicable SOP (15/Jan/2016) on 16 May 2016.
Batch release had to be done by the Head of the Quality Unit.

For QA review only an incomplete specimen copy was given in the SOP. Further information was given, that every unit should prepare the same by including respective details of formulation / product parameters which are to be checked during the release. General checklist was prepared by Meditab used for all products on site. QC

records were also reviewed as part of the approval process of batch release. However, form for the review was not part of the relevant SOP.
A checklist for verification of QC report, based on CQA-301/CL1/3 was available but was not part of the release procedure. Clear information with regard to the verification of data integrity for the relevant QC data was missing. This was resolved in the company's CAPAs.

Finished Product Specification for the product was available (FCL0066, 30/April/2013) and found in compliance with the current Certificate of analysis. However, specification for microbiological analysis was missing.
Additional document with regard to the microbiological examination was available (FCL0066A, 30/April/2013; test for TAMC, TYMC, absence of E. coli, Salmonella, Pseudomonas aeruginosa, Staph. Aureus; bile tolerant gram negative bacteria). This gave the information, that the testing should only be done on one in 10 batches or once in a year. This information was missing from the CoA.
Analytical test report for microbial testing was available, but not part of the QC records. Testing was finalized on 2 June 2016.

Raw materials
Documentation for Magnesium stearate and Nevirapine was checked.
Manufacturer for Magnesium stearate was Mallinckrodt Inc., St. Louis, U.S.A. (Name of the company was changed to Covidien).
Release for the batch used in production was documented on 09 September 2015.
Nevirapine was released on 17 April 2016 after retesting.
Additional testing for polymorphic identity was done by XRPD at Cipla Verna site together with the first release (testing on 30/Jan/2015, release on 12/Feb/2015).
A CoA from the supplier (Shanghai Desano, Binhai Road) was available.

16. Good practices in production

No cytotoxic / hormonal / beta lactam antibiotics products are manufactured at this site. Details of production and production documentation were evaluated by the inspectors during the visit of the area.
This section was acceptable overall but documentation with regard to the process parameters of the fluid bed dryer was done without double check be second operator. This issue was resolved in company CAPAs.

Reprocessing and Reworking
The procedure "Reprocessing / Reworking of the batch" (26/Nov/2015) was available. According to the SOP it only should be performed in exceptional cases. For WHO products, it was not done according to the information given by Meditab.
The need for risk evaluation, pre-approved work instructions / record forms, establishment of in-process checks, additional validation and stability studies was taken into account.

17. Good practices in quality control

There were 8 analysts allowed to do chromatographic analysis (preparators) and there were 4 operators in HPLC. There were 2 reviewers in chromatography and 2 chemical reviewers. The total number of staff in QC was 52.

The quality control laboratory was inspected and the data stated that was verified for various prequalified product's.

Inspection of computerized systems:
-There was no time and date showing on the computer screen.
-The administrator had deletion rights in Chromeleon.
-Several analyses were seen to be outside of the normal regulated folders. These were from different periods and adequate explanations were obtained from the company.

The OOS for Praziquantel Batches 4252 and 4253 was reviewed. The name of the run was FINISHED_PRODUCT\Jun\I-127\PRAZI DP 17 B\F PRAZI DP Q3 without the peak in the placebo but the peak observed in the sample (current analysis). The company stated in their report "Checked the previous analysis and sample of current analysis and found comparable response for the peak at RRT 0.12". The analysis being referred to here was done on I-082, available under "Finished Product" folder for June FINISHED_PRODUCT\Jun\I-082\PRAZI DP 07 B#14 PLACEBO MT1403581. Manoj 2482 was logged in. The explanation was generally logical and well documented.

Stability results were requested for batches KT 4252 and KT4253. This was reviewed, including those for batch KT255 as well. A discrepancy was noted in the description of tablets appearance, where the color orange disappeared from the description of the 24 month time-point for all batches loaded on stability. The company stated that this was due to the analyst changing the description to the actual description. This was not covered by any change control and this remark was made to the company.

The SOP entitled "Data organization procedure for Chromeleon software", issued on 7 April 2016 and effective since 6 May 2016, was reviewed. This was a Cipla Corporate SOP. It contained instructions to copy sequences. This operation needs to be reviewed because although the instructions are quite specific, there is one step (2.5.3.6) , where the option of pasting "sample data only" or "All (incl. raw data) appears. This means that an analyst could reuse existing test results. Events of "Copy" were seen in the instrument history for Chromeleon 2016.

The previous version of the SOP, entitled "Data organization procedure", No. DOPCS001, version No. 4, effective since 28 January 2016, was also reviewed. It was lacked detail on the following instructions, regarding the use of the "Temporary" directory:"

> *"3.4.19 Under the "Temporary" directory create the directory for the year e.g. 2013. Further create date wise folder and restore the report definition files sent from Corporate and copy the required sheets to the respective templates".*

There was no explanation on what exactly this directory can be used for. Since approximately 47 analyses were found on this folder in a disordered fashion, the use of this folder should have been better defined. Normally data should have been saved under "Sequences" in both versions of the SOPs.

The analytical reports for KT3203 Duovir-N, manufactured on 05.2013 were requested because on Day 1, electronic data was found in unregulated folders. The report was reviewed and was noted to contain an incident report. The error was described as "Sequence Duovir N RS(L2)-20-B got interrupted at Blank No. 14 and 15 for sample run. This was reported on 21.05.2013, at 8:20. It stated that during investigation checked the sequence and observed that sequence is prepared up to samples and as per specification sample to be injected freshly so analyst started the sequence using delay option but he has not calculated the time correctly because of which both sample 1 & 2 were got interrupted."

Acitab-400 DT, manufactured on 08.2012, batch No. KT2298, was reviewed but there were no chromatograms in this analytical report ; it was tested only recently to change the specifications. AR No. MT205014.

The example of Duovir N dissolution test sequence DUOVIR N DISSO 21 B.SEQ, for batch number KT3203, was reviewed. It was for AR No. MT13303313 and MT1303354, and was found on the "Rou tine" folder under "Temporary". The first chromatogram of blank was injected at 20:37 on 21.05.2013 and there was an incident report filed on 23.05.2013 again because of fresh sample not being added in a timely manner. The incident report was verified and found acceptable.

The software functional head was S. Patil. Only he had access to the Temporary folder which is software validation sequences received from Corporate. This is where they are supposed to be stored until checked for completeness. There are times where there is LAN failure, then sequence gets stored there temporarily. He stated that these sequences are incomplete sequences.

Computer system validation

Computer system validation was reviewed. This included verification of the ability to move, rename or delete the audit trail from the software. There was also a privileges distribution chart of Chromeleon software, dating from 20.06.2016. It included a documentation of system configuration for "CMUSER", seen as "Mahesh 1250". This chart showed that there were only 2 administrators in Chromeleon, Lalasaheb 14453 and Mahesh 1250.

According to the Chromeleon user manual:
The foundation for record protection is a secure operating system that provides positive user tracking and prevents unauthorized access to computers and files. Dionex recommends the use of Microsoft® Windows with the NTFS file system.

The next layer of protection is a secure relational database platform, which ensures that even those users who have access to files at the operating system level cannot read or modify records through means outside the secured application. Dionex recommends the use of Oracle® or Microsoft SQL Server as the relational database platform for secured, multi-user environments.

User management policy was reviewed.

In the document entitled "Validation of security controls of workstation", with the effective date of 14 March 2016, the access to the "network neighborhood" was verified. The "Delete option for the data" was also verified. This was stated to have been tested for the analyst, Mr. Sanjay Patil although this was not stipulated in the document.

The server computer was looked at and the inspector was told that the domain server was not a Meditab but at Cipla corporate. There were 3 dates appearing in the audit trail for changes to user configuration privileges in Chromeleon: 12.2014, 26.09.2014 and 10.05.2016.

Method validation

The method for lamivudine, Zidovudine and Nevirapine tablets was validated in 2005. It was stated that "solution stability was monitored to check the stability of known, single maximum unknown impurity, total unknown impurities and total impurities in solution state. A sample solution was preserved over a period of

1,2,4,8, 12, 16 , 20 and 24 hours and analysed. It was stated that the results are comparable and hence the solution is stable up to 24 hours. When staff was asked about this, it was stated that it was due to some sequence being ran overnight.

Stability studies

It was stated that the person in charge of stability was employed since last week only.
According to the stability sample pull out log dated of 01.06.2016, acyclovir tablet BP200 mg KT3291 strip AR MT1603068, Aciclovir tablet BP 800 mg KT3282 strip, AR number MT1603069 and acyclovir dispersible tablets 200 mg MT1603079 were withdrawn from their chambers on 01.06.2016, 01.06.2016 and 13.06.2016, respectively. Atenolol tablets BP 100 mg, batch No. KT4254, AR No. MT1603082, 25/60 30 month 07 time-point was taken out of the chamber on 07.06.2016.
Duovir N (for WHO) KT 2482, 30/75%RH condition in "container", 30 month timepoint, was withdrawn on 18.06.2016 (120 tablets). Dispersible acyclovir tablets BP400 mg batch KG50443, AR No. MT1603093, 30/65%RH condition, blister of 5 tablets, 65 tablets were withdrawn on 08.06.2016.

The number of samples in the 30°C/75%RH stability chamber was counted. The following was seen:
-Praziquantel bottles of 500 tablets (batch number not noted).
-15 bottles of Lamivir 150 on shelf R2T3
-10 bottles of Lamivir 150 on shelf R2T2
-13 bottles of Lamivir 150 on shelf R2T4
-19 bottles of Duovir N on R2T5, KG60222, expiry date of 04/2016
-16 bottles of Duovir N on R3T5, KT3343, manufactured on 08/2013.
-13 bottles of Duovir N on R3T3, KT3202, manufactured on 05/2013, expiry on 04/2016.
-13 bottles of Duovir N on R3T2, KT3201
-17 bottles of Duovir N, manufactured on 12.2013, KT3482
-15 bottles of Duovir N, manufactured on 01.2015, expiry date of 12.2017, R8T1

The monthly stability samples pull out log for June 2016, showed glucoside tablets 6 month timepoint as having been pulled out on 06.06.2016. This was the only product in the chamber in June, according to this log.

The monthly stability samples pull out logs for May and April 2016 were also reviewed. Nifedipine slow release was the only other product who was submitted to the 40/75% RH condition (Batch KG60041, MT1601931). It was initiated on 15.02.2016 with a due interval of 2 months taken on 18 April 2016. Praziquantel was the last WHO product stored in this chamber. It was withdrawn on 06.04.2016 according to the log.

The post approval stability protocol for Praziquantel tablets USP 600 mg (for WHO), which was submitted to WHO (according to the company) was reviewed by inspectors. It stated that 2 packs should be submitted to stability studies: 100 tablets and 500 tablets.
The post approval protocol only stated that the first three batches and "subsequent batches" would be tested, without specifying how many. This protocol was dated from 24 September 2014. It stated that 80 tablets would be taken per sample. This was not sufficiently specific.

Metolar-100 BP KGG0128 and zovax-800 KGG0181 were the products found in the 40/75% chamber.

The preapproval protocol, was shown afterwards to the inspector. It contained the 40oC condition, while the post approval one did not.

There were no samples in the 40^{o}C/75%RH for WHO. Only 2 products were seen to be physically present in the chamber .

There was a total of 8 probes in each chamber. They were electronically monitored and alarmed to security personnel.

For Duovir N, according to the June 2016 log, only one batch was due to be pulled out on that month and this was done on KT2483, 30 month time point, with a sample of 120 tablets on 18.06.2016.

Praziquantel batch KH505750 was also pulled out from 30/65%RH condition on 6 April 2016 due to a failure obtained at 30/75%RH. 2 batches of Praziquantel were loaded in 2015 in the 30/75%RH chamber.

The SOP 105 on stability, stated that for continuing stability batches, the timepoints should be 6, 12, 24, 36 months. This was stated to match the ICH requirements. For established products, testing timepoints are of 12, 24 and 36 months.

Microbiology laboratory

The microbiological laboratory was well equipped and accessible via personal airlock. The second airlock had to be passed to enter microbiological testing area. Biosafety cabinets with HEPA filters were available.
The incubation area was equipped with 3 dual chamber incubators for different incubation temperature ranges. An autoclave for media preparation was installed.

Overall, the quality control laboratory had adequate facilities in form of space, equipment, reagents and chemicals to test all starting material, packaging materials, intermediates and finished products before release for use or distribution.

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, Meditab Specialties Pvt Ltd, 352, Kundaim Industrial Estate, Kundaim, Goa 403 115, 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
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
   http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
   http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. 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

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