World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Manufacturers Details	
Company information	
Name of manufacturer and address	Mylan Laboratories Limited, Unit-9 Plot No: 5, Road No: 12, J.N. Pharma City, Tadi Village Parawada Mandal, Visakhapatnam – 531021 Andhra Pradesh, INDIA. North latitude: 17.670087° East longitude: 83.076092° Data universal numbering system (D-U-N-S): 86-249-9912
Corporate address of manufacturer	MYLAN LABORATORIES LIMITED Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad-500034 Telangana, India. Web: www.mylan.in
Inspected site	
Address of inspected manufacturing site if different from that given above	As above
Manufacturing blocks	MB I, MB II, MB III, MB IV (stand-alone facility for during intermediates) and MB V
Manufacturing license number	The site has a license to manufacture (for sales and distribution) wide range of APIs and Intermediates under different therapeutic categories by the Director, Drugs Control Administration, Government of Andhra Pradesh under the drug license in Form-26 bearing the manufacturing license number:07/VP/AP/2009/B/R/CC.
Inspection details	
Dates of inspection	17 - 21 July 2017

<table>
<tr><td>Type of inspection</td><td>Routine</td></tr>
<tr><td>Introduction</td><td></td></tr>
<tr><td>Brief summary of the manufacturing activities</td><td>The manufacturer was involved in the manufacturing, packaging, labeling, testing and storage of the APIs and finished dosage forms.</td></tr>
<tr><td>General information about the company and site</td><td><u>History:</u>
• Manufacturing site was established in June 2009 as Vivin Laboratories Pvt. Ltd. (Unit-2)
• Acquired by Matrix Laboratories (Mylan Laboratories) in December 2009
• Renamed as Matrix Laboratories Ltd. Unit-9 in January 2010
• Renamed as Mylan Laboratories Ltd. Unit-9 in October 2011.
<u>Main Activities:</u>
The site has five manufacturing blocks (MB-1, MB-2, MB-3, MB-4 and MB-5) The facility is designed for the manufacture of Active Pharmaceutical Ingredients and Intermediates. The manufacturing process is a chemical synthesis involves unit operations like crystallization, purification, filtration and drying steps.</td></tr>
<tr><td>History</td><td>The site has been inspected by the following authorities:
<table>
<tr><th>Authority</th><th>Last Inspection (s) Date</th></tr>
<tr><td>World Health Organization (WHO)
Geneva, Switzerland</td><td>January 2015
&
December 2011</td></tr>
<tr><td>U.S. Food and Drug Administration (USFDA)
US</td><td>April 2015
&
July 2012</td></tr>
<tr><td>Therapeutic Goods Administration (TGA)
Australia</td><td>December 2013</td></tr>
<tr><td>Austrian Agency for Health and Food Safety (AGES), Austria</td><td>16.11.2011</td></tr>
</table></td></tr>
<tr><td>Brief report of inspection activities undertaken</td><td></td></tr>
<tr><td>Scope and limitations</td><td></td></tr>
</table>

Areas inspected	• Pharmaceutical Quality System • Documentation system • Production System • Facilities and Equipment System • Laboratory Control System
Restrictions	• Inspection was focused on production and quality control of the API under assessment - APIMF280 Etravirine • Microbiological laboratory was not inspected
WHO product numbers covered by the inspection	• APIMF072 Zidovudine (manufactured at MB I and MB V) • APIMF 155 Lumefantrine (manufactured at MB II) • APIMF 166 Piperaquine tetraphosphate tetrahydrate (manufactured at MB III) • APIMF280 Etravirine **Under assessment** (stage 1 & 2 manufactured at MB I and MB IV, stages 3 & 4 & 5 manufactured MB III)

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
AQL	Acceptance quality limit
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FG	finished goods
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
ID	identity
IR	infrared spectrophotometer
IPC	In process control
IQ	installation qualification
KF	Karl Fisher

LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NIR	near-infrared spectroscopy
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	preliminary hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
PW	purified water
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QMS	Quality management system
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
RH	relative humidity
RM	raw materials
RS	reference standard
SAP	system applications products for data processing
SFG	semi-finished goods
SOP	standard operating procedure
STP	standard test procedure
T	temperature
TAMC	total aerobic microbial count
TFC	total fungal count
TLC	thin layer chromatography
TMC	total microbial count
TOC	Total organic carbon
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
WFI	water for injection
WS	working standard

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

Brief summary of the findings and comments

1. Pharmaceutical quality system

In general the system for managing quality encompassed the organizational structure, procedures and processes. There were QA and QC departments that were independent of production. In general deviations from established procedures were documented and explained. Procedure was in place for notifying responsible management of regulatory inspections, serious GMP deficiencies, product defects and related actions.

The traceability of records and documentation system were satisfactory.

TrackWise system was used for:

- Incidents
- Change controls
- OOS/OOT investigations
- Complaints investigation
- CAPA tracking

Product Quality Review (PQR)

The SOP "Annual product review / product quality review" was discussed. The PQR covered but was not limited to:

- Intermediate / API manufacturing overview
- Review of packaging materials
- Review of API starting materials
- Review of intermediate manufacturing
- Final API review
- Process capability determination
- Review of manufacturing supporting systems
- Review of status on DMF deficiencies
- Review of pending CAPA or other action items from previous PQR
- Final conclusion / recommendations.

PQR was performed annually and according to the SOP should be completed by the end of February of the following year.

Process capability was evaluated by statistical process control (SPC) by Cpk. Process capability was calculated using Minitab software.

PQR report for Zidovudine (ZDU) review period January 2016 to December 2016 and PQR Report for Lumenfantrine for review period from January 2016 to December 2016 was discussed.

A review on Equipment Qualification, Supporting System – Water and Compressed Air was reported in Annual Review of Manufacturing Supporting Systems.

Quality risk management (QRM)

The SOP Quality Risk Management was discussed. The tool used by the company in managing risk is by FMEA. The classification of RPN was based on;

- Severity; Fundamental, High, Moderate, Minor and Insignificant
- Detection: Not aware / No control exists; Nonexistent / Very little chance of detection; Not effective / Likely to be detected; Effective / Very likely to be detected; Very effective / 100% likelihood of detection
- Occurrence: Almost certain, Likely, Possible, Unlikely, Rare

Based on the procedure, the risk management should be reviewed every 3 years and an annual plan was established 'Annual Schedule of Quality Risk Management Reports Year: 2017'. The risk assessment was conducted based on product manufacturing process, as shown to the inspectors for Etravirine API.

Deviations

The SOP "Handling and investigation of incidents / deviations", its flow chart and register were discussed. Definition of incident was "any atypical event or deviation which is not intended or expected, occurs during the manufacturing, packaging, testing or release product for cGMP materials". According to the SOP incidents / deviations were classified as:

- Minor
- Major
- Critical

Incidents / deviations were classified by Quality Assurance Department (QAD) personnel.

A number of deviation investigation reports were discussed. Deviations were trended quarterly, trends for 2017 were presented to the inspectors.

According to the SOP the following tools were used to establish root cause:

- 5 Why`s (used for human errors)
- Ishikawa diagram
- Cause / effect diagrams

Corrective actions and preventive actions (CAPA)

The SOP "Corrective and preventive actions with effectiveness check", flow chart and register for 2017 were discussed. The SMP was applicable but not limited to:

- Deviations
- OOS/OOT
- Validation /qualification
- Complaints
- Recall
- Self-inspection/external inspection
- Risk assented

- Returns
- Management review

According to the SOP, CAPAs were proposed by cross functional team. CAPA implementation was monitored by QAD personnel.

Change control (CC)

The SOP "Change management process", change approval flow chart and registers for 2016 and 2017 were discussed. Impact assessment and risk assessment was applied for CC. CCs were classified as:

- Minor
- Major
- Critical
- Temporary
- Permanent

CC effectiveness checks were performed after defined period of time to ensure implementation was satisfactory. CCs were trended quarterly, trends for 2017 were discussed.

A number of CCs were discussed.

Management review (MR)

The SOP "Management review" was discussed. According to the SOP management reports were prepared monthly. The following items should be covered:

- Self-inspection
- Audits
- Validation status
    - Process validation
    - Cleaning validation
    - Equipment validation / qualification
    - computer system
- Technical agreements
- Training
- Preventive maintenance of the equipment
    - Production
    - Quality control
- Calibration of equipment
    - Manufacturing
    - Quality control
- Documentation
- Quality incidents
- CAPA
- CC
- Analytical investigation reports
- OOS
- OOT

- Rejections
- Reprocessing
- Stability
- Recalls / withdrawal
- Health authority notifications
- Complaints
- APQR/PQR

Monthly meeting minutes were presented to the inspectors.

Complaints

The SOP "Handling of customer complaints", its flow charts and register were discussed. Designates person from site QAD was responsible to log the complaint in TracWise system. Complaints were classified as:

- Critical
- Major
- Minor

Site Quality Head was responsible for complaints investigations. A number of complaint investigation reports were discussed.

Recalls

The SOP "Product recalls" was discussed. There were no product recalls in Company history. Recall effectiveness was evaluated by mock recall. Site Quality head was responsible for recall on site level. Recalls were not classified.

According to the SOP a mock recall should be performed once in three years. Last class III mock recall was performed in March 2017 for export and local market. The Company dispatched APIs directly to finished product manufacturers or agents. In order to execute a recall, the Company traced dispatch details in SAP system.

Self-inspection

The SOP "Internal quality audit" and schedule for 2017 were discussed. The following departments were under self-inspection program:

- Stores
- Manufacturing
- Solvent recovery plant
- Engineering
- Quality control
- Quality assurance
- Personnel & administration
- Information technology

A number of self-inspection reports were discussed.

Supplier qualification

The SOP "Vendor approval" and its flow chart and vendors audit schedule for 2017 were discussed. Vendors were identified by supplies chain management. According to the SOP all key starting materials (KSM) vendor should be audited once in 3 years. Audits were performed by the corporate QA.

Approved suppliers list and supplier audit schedule for 2016 & 2017 were presented to the inspectors. Profile folders were maintained for each supplier; annual supplier-specific quality reviews were conducted.

Personnel

The current organization chart of the company was available. The company had sufficient number of personnel with responsibilities according to their respective unit and department. Personnel were wearing suitable clothing for the manufacturing activities.

The SOP "Training of employees" and its flow charts were discussed. This procedure was general and explained training for new and existing employees. Training effectiveness was evaluated by multiple choice questionnaires. During inspection it was discussed that consideration should be taken into account to introduce open questions as part of the training effectiveness evaluation.

Job description and training records for Mr XX, responsible for release of APIs/intermediates was discussed. List of authorised personnel to release the dispatch batches was presented to the inspectors.

The SOP "Qualification of analysts" and its flow chart were discussed. According to the SOP analyst shall be qualified after joining, as per allotted job role(s) and prior to perform new techniques. Experienced analyst re-qualification was performed once in a three years. New analyst was given to analyze approved sample, results were compared. RSD values for triplicate tests were specified.

Mr. XX qualification for HPLC tests (relative substances and assay) raw data was discussed.

2. Documentation system

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures.

Production, control and distribution records were retained for one year after the expiry date of the batch. For APIs with retest dates, records were retained for three years after the batch was completely distributed. Specifications were established for raw materials, intermediates and APIs. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories.
The Company had a policy to archive all logbooks and other documents.

3. Production system

In general production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Deviations from procedures were recorded; major deviations were investigated. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use.

Inspection was focussed of facilities and equipment used for manufacture of Etravirine API validation batches. Etravirine API was manufacturing was carried out in V stages.

Closed systems were used for materials transfer from reactors to centrifuges. Manual operations were also applied, e.g. uploading materials from centrifuges, drying and packaging. Dedicated centrifuge bags, sieves and product transfer pipelines were used for all products.

A number of solvents were received and stored in outside tanks. Samples were taken from tankers, after release solvents were transferred to the storage tanks. Fresh solvents were mixed with solvents remaining in tanks and again samples were analysed.

A number of solvents were received and stored in drums. Solvents in drums were sampled in dedicated sampling area having air filtration through 0.3 micron filter and exhaust connected to scrubbing system.

Solid starting materials and packaging materials and finished goods were stored in the same warehouse in different locations.

The batch numbering was given as per API stage and described in the SOP Batch Numbering System.
A register was kept for the issuance of MBPR, "MBPR Issue & Retrieval.

Reprocessing and Reworking
The SOP for Reprocess was discussed. According to the SOP reprocessing could conducted only once and must be initiated through Change Control.

The SOP for Reworking was discussed. Based on the procedure, for any decision for reworking, the changes in the manufacturing process must be validated. Any reworking activity should be registered in Rework Log Register.

4. Facilities and equipment system

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups and contamination.

Permanently installed pipework was appropriately identified. Solvents pipelines had different colour codes.

Equipment status boards indicated associated equipment calibration status, dues data and preventive maintenance due date. Equipment was identified as to its contents and its cleanliness status.

"Temperature mapping study" and "Protocol for temperature mapping study – Finished goods warehouse" were discussed.

Utilities

Purified water system (PW) No 1 was inspected. PW system was installed in 2010. PW was used for cleaning equipment, tools and production. PW was in continuous circulation at ambient temperature (T). Conductivity and flow rate were checked on line at the return loops. Designed flow rate NTL 1.2 m/sec. System had 2 loops. PW storage tank and loops were sanitized every 15 days using 80 – 85 °C hot water for 30 minutes. PW storage tank and loop were made from stainless steel 316 L. PW system was well maintained.

PW microbiology trends for sampling points after return loops were discussed. Trends were prepared monthly. Action and alert limits were specified. Trends for 2016 was under review – draft trends were presented to the inspectors.

Air handling unit AHU 301, supplying air to MB III clean rooms was inspected. Re-circulated air was used in clean rooms. Primary filter was G3, secondary G4, HEPA filter H13 was installed in plenum. Pressure differentials between G3 and G4 and G4 and H13 were monitored. HEPA filters integrity tests were performed once per year.

Nitrogen was produced on-site and stored in the compressed gas form. Oxygen monitoring was done on line. Chemical and microbiological tests were performed every six months. Nitrogen was filtered via inline disc filter. Nitrogen production was not followed up during this inspection.
Oil free compressed air was used in contact with product. Compressed air in contact with product was filtered via 0.01 micron filters. Compressed air production was not followed up during this inspection.

Chemical and microbiological tests of compressed air and Nitrogen were performed every six months by contractors.

Environmental monitoring (EM)

EM trends were prepared quarterly. Trends, settle plates and active air sampling for clean rooms MB III, Module I for 2016 were discussed. EM samples were collected during one day once per 3 month. Action and alert limits were specified. Settle plates were exposed for 4 hours.

5. Laboratory control system

In process control (IPC) analysis were performed in Quality control laboratory.

The SOP “Investigation of out of specification (OOS) results” and SOP “Investigation of out of trends (OOT) analytical results”, their flow charts and OOS trends for 4th quarter 2016 and 1st quarter 2017 were discussed. OOT trends for 2nd quarter 2017 were discussed. OOS register for 2016 and 2017 were presented to the inspectors.

A number of OOS investigation reports were discussed.

The SOP "Management of reference and working standards (WS)" and its flow charts were discussed. According to the SOP WS were qualified against the Pharmacopeia reference standards (RS). WS were dispensed in 14 amber vials. One vial was used for one month. Dispensing was performed under LAF. In case RS were not available in-house reference standards were prepared.

Reference standards were stored in two fridges at 2 - 8 °C T. T in fridges were recorded once per day.

Excel sheets were used for assay and impurities calculations. It was said that excel sheets were validated, validation protocol/report were not checked.

Etravine API validation batches were manufactured in 2014. At that time HPLCs and GCs were connected to the Empower 2 software. Therefore analytical raw data was retrieved from the server. Analytical electronic raw data for the validation batch No XXX starting from the stage I was compared with hard copies. Also 6M stability studies were compared for the same batch.

API reserve samples were retained for one year after the expiry date and stored in the same packaging system in which the API was stored. Reserve samples for APIs with retest dates were retained for three years after the batch was completely distributed.

6. Qualification and Validation

Process Validation

The Process Validation and Validation Master Plan were discussed. Based on the VMP, equipment routine requalification will be conducted for every 5 years for direct contact equipment. Process validation protocols / reports for Etravirine were discussed.

Cleaning Validation

The Cleaning Validation (CV) Cleaning Validation or Verification was discussed. It was conducted prior to every stage of API manufactured and was initiated by "Product Changeover Request Form. The sampling technique was based on swab sampling and rinse sampling. A register was initiated for monitoring the CV conducted in "History of Cleaning Validation for Product Changeover".

The CV for Change over from XX to YY was discussed. Cleaning was preformed using purified water and methanol. A number of cleaning validation protocols / reports were discussed.

Computer System Validation

The Empower 3 Computer Validation was discussed. The documents related to the validation were reviewed and discussed.

The risk assessment was conducted unto the system based on severity impact tools, which were further categorized as;

- Likelihood of impact
- Severity of impact
- Mitigation Control

The challenge for user privileges was done under "Verification of Access Controls in Empower 3". An established validation plan Computer System Validation Plan – Installation Qualification was discussed. Five access levels were specified.

Back-up of electronic data

All online laboratory data through the Empower 3 system was backed up as described in procedure Empower 3 Data Backup, Restoration and Verification. Disaster Management procedure for GxP Computerized Systems was in place, the back-up copy was also kept at the Corporate Office located in Hyderabad. Back-ups were registered in "Empower 3 Electronic Data Backup Log".

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, as well as corrective actions taken

- APIMF 072 Zidovudine
- APIMF 155 Lumefantrine
- APIMF 166 Piperaquine tetraphosphate tetrahydrate
- APIMF 280 Etravirine

manufactured at Mylan Laboratories Limited, Unit-9 (manufacturing blocks MB I, MB II, MB III, MB IV, MB V) located at Plot No: 5, Road No: 12, J.N. Pharma City, Tadi Village Parawada Mandal, Visakhapatnam – 531021 Andhra Pradesh, INDIA was considered to be manufactured in compliance with applicable sections of WHO GMP for Active Pharmaceutical Ingredients.

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 used for assessing compliance

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

2. 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/
   Short name: WHO TRS No. 986, Annex 2

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

4. 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
Short name: WHO TRS No. 970, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

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

6. 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
Short name: WHO TRS No. 961, Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

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

9. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
Short name: WHO TRS No. 957, Annex 3
http://www.who.int/medicines/publications/44threport/en/

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

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

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

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

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

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

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

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

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

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the 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
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. 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
Short name: WHO TRS 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
Short name: WHO TRS 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
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf