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Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Macleods Pharmaceuticals Limited
Corporate address of manufacturer	G-2 Mahakali Caves Road, Shanti Nagar, Andheri (E), Mumbai 400 093, Maharashtra, India
Inspected site	
Address of inspected manufacturing site if different from that given above	Address of Site : Plot No.: 2209, GIDC, Sarigam-396155, Dist Valsad, Gujarat State, India Latitude: 20°18.436' N & Longitude: 72°50.987' E
Unit/block/ workshop number	Unit V
Manufacturing license number	Manufacturing license: G/25/1759, G/28/1405 GMP Certificate: 1503484 (FDCA Gujarat)
Inspection details	
Dates of inspection	8-12 August 2016
Type of inspection	Routine
Introduction	
Brief summary of the manufacturing activities	The Unit -V was designed for manufacturing of Active Pharmaceuticals ingredients (APIs) and intermediates. The site was established in year 2007. The manufacturing blocks were used for multi-products production except a dedicated facility for manufacturing of Levothyroxine Sodium.
General information about the company and site	The Macleods Pharmaceuticals Limited was established in year 1989 for production of pharmaceuticals products. Finished dosage forms and active pharmaceutical ingredients are manufactured in 7 different units. The corporate office with the R&D center is located in Andheri Mumbai.
History	• 12/06/2012-14/06/2012 WHO Geneva • 11/09/2012 FDCA Gujarat and CDSCO India • 13/08/2013-16/08/2013 Korean FDA • 26/05/2014-29/05/2014 WHO Geneva

	• 22/01/2015 FDCA Gujarat and CDSCO India
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	• Quality management • Personnel • Buildings and facilities • Process equipment • Documentation and records • Materials management • Production and in-process controls • Packaging and identification labelling of APIs and intermediates • Storage and distribution • Laboratory controls • Validation • Change control • Rejection and reuse of materials • Complaints and recalls • Contract manufacturers (including laboratories) Site visit: • Block G • Warehouses • Quality Control Labs • Stability chambers • Purified Water plant
WHO product numbers covered by the inspection	APIMF103 Ethionamide APIMF150 Tenofovir Disoproxil Fumarate (TDF) APIMF 165 Emtricitabine APIMF 182 Cycloserine APIMF 256 Oseltamivir Monophosphate APIMF 269 Terizidone APIMF 272 Aminosalicylate Sodium APIMF 275 Levofloxacin Hemihydrate APIMF 300 Pyrazinamide APIMF 303 Atazanavir Sulfate APIMF 305 Linezolid APIMF 312 Ethionamide

Abbreviations		
	AHU	air handling unit
	ALCOA	attributable, legible, contemporaneous, original and accurate

API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance

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

Brief summary of the findings and comments

1. Quality management

Responsibilities of the Quality Unit(s)

There was a benchmarking system in place within the corporate to assure harmonized QA policy within the corporate. Besider, there were QA functions shared between the corporate and local QA, e.g.internal audits, evaluations (change control, OOS, quality complaints), material management system, vendor audits, product and method development, software validations.

The departments and personnel responsible for quality assurance and quality control were independent from the production. Responsibilities of QA and QC were well described, including in position descriptions for key staff. The position descriptions reviewed were detailed.

Responsibility for production activities

The Plant head had overall responsibility for managing production activities and there was a manager for each of the production block. Responsibilities were well described. The position descriptions reviewed were detailed.

Quality Risk Management

- There was a procedure for Quality risk management. Various approaches to risk assessment were allowed. The Risk analysis report for Block G and Risk assessment study for manufacturing process of APIs were reviewed. It was acceptable generally.

Deviations

A procedure for handling deviation was reviewed. Deviations were classified into unplanned and planned. Unplanned deviations were classified into critical, major and minor in the procedure. Annual deviation review in 2014 was checked. CAPAs were proposed according to an SOP. Non-compliances observed during the inspection that was listed in the full report regarding root cause investigation and analysis were addressed by the manufacturer to a satisfactory level.

Product Quality Reviews (PQRs)

The PQRs were prepared according to an SOP and summarized the following information.

- Product General Information.
- Review of Key Starting Material and Intermediates Quality.
- Yield.
- Finished Product Quality and Yield.
- Review of Critical In-process parameters.
- Review of Critical equipment qualification status.
- Review of Environmental conditions during manufacturing in classified area.
- Review of changes, deviations and related investigations.
- Review of OOS/OOT data and related CAPA.
- Review of Stability Studies.
- Review of Complaints, Returns, Recalls with related investigations and corrective actions.

The Product Quality Reviews of 2015 for TDF, Cycloserine, Emtricitabine, Pyrazinamide and Linezolid were reviewed during the time of inspection.

Product release

The QA head and the Deputy QA head was responsible for the product release of APIs and intermediates according to an SOP. The following documents were prepared:

- BPCR checklist
- Finished Product packaging and releasing checklist
- Analytical Raw data checklist

Following to the assessment of the above information the status change is recorded in the ERP system, QA release label is issued and Goods Transfer Note is prepared for the warehouse.
The release records of a Cycloserine batch were discussed.

2. Personnel

Personnel qualifications

There were a sufficient number of personnel who were suitably qualified through qualifications, experience and training. Responsibilities were well described, including in position descriptions for all personnel. There are approximately 828 employees and 256 temporary contract employees at the site.

Personnel hygiene

Personnel were required to wear protective clothing suitable for the type and stage of manufacturing. Suitable sanitation and change room facilities were provided. Smoking and eating was not permitted in manufacturing areas.

Training

Training was required to be conducted on an initial and ongoing basis according to an SOP. The training requirement for formal and contract staff were specified. A training plan for each individual staff was available. The effectiveness of training was evaluated according to the procedure. A selected sample of training records was reviewed.

3. Buildings and facilities

The buildings was constructed using ferro-concrete material. Walls and ceilings in powder processing areas are painted with epoxy paint, while in the other areas like other manufacturing, warehouse and quality control areas with enamel paint. Sharp corners were avoided.

The site information of different blocks were documented and provided by the company.

HVAC system

HVAC system provided filtered air to pharma areas of Block G (final synthesis, drying and packaging of APIs) to meet requirements for a Grade D environment. Specifications included pressure differentials were documented. Microorganisms and particulates were regularly monitored but not checked in detail.

Water system

Purified water (PW) was used in the final stages of API manufacturing. The PW system located in block G was inspected. The system was a design using double reverse osmosis and EDI to produce PW. PW was controlled the temperature below 25^0C and distributed by a SS 316L loop. The water system appeared to be well maintained and the results of regular monitoring indicated that it was under good control. The design qualification and OQ testing results were spot checked and found satisfactory generally.

Containment

The final synthesis, purification and packaging of APIs took place in non-dedicated facility. In areas where dust might be produced (e.g. milling), the area was maintained at negative pressure to adjacent areas. Non-compliances observed during the inspection that was listed in the full report regarding the likelihood of across-contamination were addressed by the manufacturer to a satisfactory level.

4. Process equipment

Design and construction

Equipment used in the manufacture of APIs appeared to be of appropriate design and size for its intended use, cleaning and maintenance. Manufacture and material transfer took place in closed systems wherever possible. List of manufacturing equipment are enclosed in the SMF and the validation Master Plan.

Equipment maintenance and cleaning

The preventive maintenance and filter cleaning program policy defined monthly, quarterly and half yearly activities, managed by means of annual planner. The planner was available block-wise. The maintenance planner of Block G was reviewed.

Calibration

Calibration was performed in house according to documented procedures. Measuring equipment was required to be labelled with its calibration status.

Computerized systems

Computerized systems were used for material or production control and in the QC Laboratory.

5. Documentation and records

Documentation system

The document control functions were managed by the QA department according to an SOP. The documentation system was mainly paper based but there were electronic documents also used (e.g. ERP and and chromatography softwares).

SOPs were prepared according to an SOP. The list of SOP prepared department-wise was up-to-date. The documents were archived for the pre-defined period in two archives located in different buildings.

Batch production records (batch production and control records)

The manufacturing activities were recorded in batch production and control records issued by 3 persons working for the QA department.

The batch numbers were generated block-wise, indicating the year, the block, the serial number within a year recorded in the Batch Number Issuance Record - binded logbook. BPCRs together with the ECRs (equipment cleaning records) were prepared at the site.

Laboratory control records

Laboratory control records, including a sample receiving and distribution register, and test records, were available for inspection.

Records of raw materials, intermediates, API labelling and packaging materials

Records of raw materials, intermediates, API labeling and packaging materials were maintained.

Batch production record review

Examples of completed BMRs were reviewed and found to be satisfactory.

6. Materials management

General controls

Each of every materials used and produced at the site had a unique item code requested by the Site QA, generated and entered to the ERP master list by the CQA.

Receipt, quarantine and release

The raw materials and packaging materials were received in Warehouse 2 according to an SOP. The receipt of the material was against the product order, the approved vendor list and ERP material codes and recorded in the Material Receipt Checklist.

Materials cleaned in the receipt area were first placed in the quarantine area, sampled, released then transferred to the “Released” locations. The materials stored in the warehouse were indicated in the “Rack Index” on whiteboard but not documented in ERP system or in paper document.

The dispensing of the materials was performed by the warehouse staff . The intermediates were handled according to an SOP. Only intermediates released by the QA were transferred to the Warehouse 2. The intermediates due to retest were removed from the location of the released items to the Quarantine area.

Vendor approval

All manufacturers of raw materials and packing materials were approved through vendor approval procedure. The vendor approval was carried out as per an SOP on Vendor qualification. The vendor lists were available and tally with the information available in the ERP system.

7. Production and in-process controls

Production operations

The API products in the inspection scope were operated in the specified facilities according to the information provided by the company. The blocks were generally not dedicated to the APIs in the PQ scope.

The BPCRs of Cycloserine was reviewed. The holding time of the intermediates was supported by holding time study results. The study records for cycloserine intermediate were available.

The production block G among all above production area was built since last WHO inspection and was inspected during this inspection. It was generally found to be of suitable standard, clean and logically organized to suit their intended purpose.

In-process sampling and controls

In-process sampling and testing was performed at defined stages during processing. In-process samples were tested in the QC laboratory.

Blending batches of intermediates or APIs

Blending of API batch tailings was permitted with the expiry of the shortest expiring batch allocated to the blended batch. This was not inspected in details.

The company performed drying of one batch API into two sub-lots, no blending performed after the separate drying and each lots was not individually tested. Non-compliances observed during the inspection that was listed in the full report regarding batch blending and testing were addressed by the manufacturer to a satisfactory level.

It was noted during inspection that batch number of blending or micronization batch was no link with product original batch, e.g. year in the batch number of micronized batch merely reflected the year of micronization operating time. A history of the manufacturing year in the original production batch had no immediate traceability.

Contamination control

Production of APIs took place in non-dedicated facilities. Adequate precautions to minimize the likelihood of contamination, including final stages taking place in a Grade D controlled environment, were in place. An SOP described the line clearance at product change-over. There was a checklist in place for control purposes.

8. Packaging and identification labelling of APIs and intermediates

The labelling of the materials was a function shared between the QA (status labelling), QC (sampling), Warehouse (material labels) and Production (labelling of intermediates) departments.

Packaging materials
Packaging materials were subjected to appropriate quality control testing before release.

Packaging and labelling operations
Packaging and labelling operations were appropriately described in batch packaging instructions.

9. Storage and distribution

Warehousing procedures
Finished APIs were stored in a designated warehouse and held in quarantine until released by the authorized Person. A ERP system was used to control stock and distribution.

Distribution procedures
APIs and intermediates were released for distribution after they had been released by the Quality Unit. The handling and dispatch of the finished products (API) was detailed in an SOP.

Storage qualification
The qualification, validation and change control records of a cold chamber located in Warehouse 2 were discussed. The change control for the relocation of the chamber was documented. Qualification protocol and repoert were available fo reviewed.

10. Laboratory controls

General controls
The QC department was responsible for testing of raw materials, packaging materials, intermediates, APIs, cleaning validation samples, water and release of raw materials based on an SOP. The release was recorded in the ERP system.

Testing of intermediates and APIs
Sampling was performed by dedicated staff of the QC department. The test samples entering the QC laboratories (including microbiology) were recorded in inward registers.

The quality attributes and the corresponding test methods of the manufactured products (APIs) were described in specification and standard test procedures (STP) as described in SOP on the distribution and retirement of spacifications and STPs.
The “Final Product Specification and STP Index” was regularly updated.

The specifications and STP were prepared for the following materials:

- RM (raw material)
- PM (packaging material)
- IP (in-process material)
- INT (intermediate)
- API (active substance)
- RS (recovered solvents)
- BP (by-product)

– CL (cleaning)

Reference materials were stored in control. The compendial standards were stored in a refrigerator, the working standards in a cupboard at ambient temperature. The working standards were qualified according to compendial standards. The qualification and usage records of cycloserine working standard were available.

Validation of analytical procedures

The analytical test method for related substances of cycloserine was validated.

The general and practical considerations of the HPLC testing were summarized in the Good Chromatography Practice and the general testing procedure for HPLC.

Chromatographs were connected into network managed by Chromeleon Software. Chromatographic test raw data were managed electronically.

The list of user together with the user groups and privileges was available as a printout (List authorized users) and in-line with the user list at the system. The system audit trail was appropriate to trace back the removal of an analyst (left the company in July). The analytical equipment were qualified then regularly maintained and calibrated according to QC written procedures. The annual planner of calibration also covers the maintenance which is due before the calibration. The qualification and calibration records of a HPLC were reviewed. The IQ/OQ was performed by the vendor Agilent. The maintenance and calibration is due in every 6 months by the QC personnel.

Handling of out of specification (OOS) results

The OOS results were investigated. The cases had unique identification codes and recorded in a logbook common for all materials and departments. There were 130 OOS reports recorded in 2016.

The investigation and analytical test records of an OOS on Cycloserine were reviewed.

Stability monitoring of APIs

The stability chambers were moved from the terrace floor of the Admin building to the recent location (QC Expansion Building, 3rd floor) in May 2016. The handling/management/stocking of stability samples was paper based.

Microbiological testing

The microbiology laboratory was integrated into the organization of QC and responsible for testing of water, environmental monitoring, cleaning validation and API samples.

The test specification, test methods and test records of a PW sample point SP-19 was reviewed and discussed. PW specification meets the USP/PhEur/BP/IP/In-house requirements.

11. Validation

Validation policy

The Validation Master Plan summarized the main validation, qualification and calibration functions and policies applicable for the entire site.

Process validation

Process validations were performed for all new products introduced at the site according to written protocols and recorded in reports covering critical parameter to be studied and acceptance criteria to be met.
The following validation documents for Cycloserine, TDF, Pyrazinamide and Linazolid were reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding process validation were addressed by the manufacturer to a satisfactory level.

Qualification and Calibration
Production and laboratory equipment were qualified and calibrated prior to use. Re-qualification was carried out in case significant change in process or critical equipment and/or as per pre-defined frequency of 5 year ±3 month.

Calibration of critical devices (measuring and controlling devices such as pressure gauges, temperature controllers, magnehelic gauges) was carried out according to annual schedule and standard operating procedures. Calibrated equipment/devices were identified by means of calibration tags. The calibration was performed in-house or by contract partners. The calibration records of a temperature probe and temperature controller were discussed.

There were critical computerized systems used at the site to be validated according to an SOP.
The list of computerized system contained the ID of the server, computer, the main function and the classification.
The validation records and the Excel sheets used for calculation at the QC laboratory and performed by a contract partner were reviewed.

Cleaning validation
The cleaning validation was defined in an SOP which was reviewed.
Cleaning validation in a module of Block G for product change over from TDF to Pyrazinamide as example was reviewed. Various methods for calculating maximum carry over were used, but ultimately 10ppm was used as worst case.

12. Change control
Change control was managed according to an SOP. Change control was divided into two types documents and facility related changes. Changes were classified as class minor, moderate, major.
Change control annual review in 2015 was checked. Some examples of changes regarding product batch size, specification etc. were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change controls were addressed by the manufacturer to a satisfactory level.

13. Rejection and re-use of materials
Reprocessing and Reworking
The reprocess and rework was defined in an SOP. The reprocessed/reworked batches received an additional code in the batch number and were indicated in the PQR. The QA was responsible to define study supporting the stability of the reprocessed/reworked batches.

Recovery of materials and solvents

There was an SOP described the procedure for usage of recovered solvents/substances and byproducts with manufacturing process.

14. Complaints and recalls

The complaint procedure was detailed in an SOP. The complaints may be received by the QA, the Marketing Department and the Site QA. The complaints were recorded in the Customer Compliant Log. The records of a complaint was available and reviewed.

The product recall together with the stoppage of sales and distribution was the responsibility of the QA Head, Deputy QA head as described in an SOP. There was no recall recorded since the last WHO inspection.

15. Contract manufacturers (including laboratories)

There was no contract manufacturing and testing of APIs in the inspection scope.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned. The API products covered by the inspection manufactured at Macleods Pharmaceuticals Limited located at Plot No.: 2209, GIDC, Sarigam-396155, Dist Valsad, Gujarat State, India were considered to be manufactured in compliance with 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 referenced in the inspection report

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.
   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/

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/

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
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