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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	**Cipla Ltd**
Corporate address of manufacturer	Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400013, India
Inspected site	
Address of inspected manufacturing site if different from that given above	Cipla Ltd, Unit 1, Plot A-33 & A-2 MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, India Cipla Ltd, Unit 2, Plot A-42 MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, India **GPS Coordinates:** a. Unit I: 18.52.633°N, 73.10.933°E b. Unit II: 18.52.55° N, 73.10.733°E
Unit / block / workshop number	Unit-I & II
Manufacturing license number	Unit-I: Form 26 - license No (25) 845 & (28) 707 valid until 31.12.2022 Unit II: Form 26 - license No (25) KD620 & (28) KD 435 valid until 17.08.2021
Inspection details	
Dates of inspection	15 to 18 January 2018
Type of inspection	Routine GMP inspection
Introduction	
Brief summary of the manufacturing activities	Manufacturing, quality control and batch release of: • Non-sterile medicinal products: coated/uncoated tablets, • Active Pharmaceutical Ingredients (APIs) and drug intermediates
General information about the company and site	According to the Site Master File provided and the presentation given, Cipla Limited is a public limited company established in 1935 by Dr K.A. Hamied and managed by a professional board of directors. It has its own management control & operation and has no parent company.

Cipla manufactures products of various ranges including Prescription, Animal Health care, OTC and Active Pharmaceutical Ingredients, which are supplied to over 150 countries located in the various regions including USA, Europe, Australia, South America, Brazil, Middle East Asia and Africa. It also has Research centres located at Vikhroli, Patalganga and Bengaluru. The Patalganga site has a total of 1427 personnel with 841 employed in Unit I and 586 in Unit II for both API and Formulation facility.

Manufacturing activities are carried out on the site as shown below:

Unit	Plot No.	Block	WHO PQ
I	Plot No. A-33, Plot No. A-2, and Plot No. A-37/2/2	API-I	Daclatasvir hydrochloride
		API-II	NA
		API-III	NA
		API-IV	Praziquantel
II	Plot No. A-42	API	Artemether, Artesunate, Lamivudine, Lumefantrine, Moxifloxacin Hydrochloride

History	The site has been regularly inspected by WHO-PQT. The last WHO PQ inspection on this site was performed in February 2014. The site has also been inspected by several regulatory authorities including MHRA UK, TGA Australia. Recently, the site was inspected by USFDA in November/December 2017.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients: • Quality management • Personnel • Buildings and facility • Process Equipment • Documentation and Records • Materials Management • Production and In-process controls • Packaging and identification labelling of Intermediates and APIs • Storage and Distribution

	• Laboratory Controls • Validation • Change control • Rejection and re-use of materials • Complaints and recalls • Contract manufacturers • Self-inspection
Restrictions	None
Out of scope	Only WHO products were covered during the inspection.
WHO product numbers covered by the inspection	Artemether (APIMF043) Artesunate (APIMF004) Lamivudine (APIMF001) Lumefantrine (APIMF075) Moxifloxacin (APIMF091) Daclatasvir Di-hydrochloride (APIMF328, under assessment)

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

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

1. Quality management

The quality management systems were established, documented and implemented in general. The QA and QC department was independent from production. The production and quality control procedures were defined in detailed procedures (SOPs) and were followed.

Annual product quality review (APQR) was carried out using procedure. It is a corporate procedure which is applicable to FPPs, APIs and intermediates. The APQRs are prepared on a rolling basis i.e. based on ANDA approval date to 12 month. The procedure covered aspects of quality review in accordance with the WHO API GMP guideline including product information, review of starting materials, packaging materials, critical in-process tests, critical API test results, trend analysis, deviations, batch failure, OOS/OOT, changes to process and analytical, deviations and related investigations, marketing authorization and variations, quality returns, complaints and recalls, stability monitoring programme, CAPA, equipment and utilities, validation, previous APQR comments, conclusion and follow up action.

Data was trended graphically and process capability performed. For process capability assessment, 25 batches were required. If less than 25 batches were manufactured, batches produced in the previous year were considered for the review. As a measure of process capability, if CpK was found to be less than 1.00, the production process would be reviewed and recommendation made. If CpK was found between 1.00 and 1.33, the affected parameter would be monitored and for CpK greater than 1.33 the process was considered to be capable.

Deviations were handled according to the procedure. Electronic software 'Trackwise" was used to manage deviations. Deviations were classified into major and minor basing on the impact on the quality of the product. They were further categorized into planned and unplanned deviations. Operators were expected to log in deviations in the Trackwise software within 24 hours and if longer than the specified time, provide justification.

The SOP for management review, Quality Management Review (QMR) was checked. According to the SOP, QMR meeting were held on a monthly basis at unit level and led by the Head Unit Quality; reviewing the different aspects of the QMS including product performance, technology transfer, stability study, OOS, OOT, CAPA, major changes, significant outcomes of APQR. Records for QMR for the month of 2017 were reviewed and found satisfactory in accordance with the stipulated procedure.

The SOP for organization chart and job responsibilities was reviewed together with the organogram. The records showed the quality unit that is independent of production and which fulfils both quality assurance (QA) and quality control (QC) responsibilities. Separate QA and QC units were designated for Unit-I and Unit-II given the moderately large size of the company.

Self-inspection was carried out following the procedure. The procedure provided instructions on valuation and certification of inspectors; Composition of the audit team; Planning and scheduling internal audit; Inspection for non- routine unscheduled inspection to check on specific system or area. Schedules for self-inspection for the year 2015, 2016 and 2017 were checked and found to be executed according to the plan. Key areas in the manufacturing system were inspected every six months. Checklists for API Plant, QC and Water System were viewed to verify performance of the self-inspections. Templates for Audit report and CAPA were also reviewed and found satisfactory.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Personnel

According to the records reviewed and interviews held there were an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

Job Descriptions of Key personnel for production and QA/QC for Unit I and Unit II were checked.

The responsibilities of all personnel engaged in the manufacture of intermediates and APIs were specified in writing in the respective job descriptions.

Training was regularly conducted by qualified individuals and covered the particular operations that the employee performs as well as GMP as it relates to the employee's functions. Records of training were appropriately maintained.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Buildings and facilities

The building, manufacturing departments and the facilities inspected were maintained to be acceptable in general. The flow of materials and personnel through the building or facilities were designed to prevent mix-up and cross contamination in general. The production units supported manufacturing using multi-product equipment and not product dedicated equipment.

The API manufacturing facilities for Unit I and Unit II were inspected. 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. The facilities had adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination. Laboratory areas and operations were separated from production areas.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

4. Process equipment

The equipment maintenance calibration and cleaning were performed according to the procedure in general.

Equipment used in the manufacture of intermediates and APIs were of appropriate design and adequate size, and suitably located for the intended use, cleaning, sanitization and maintenance. Surfaces of the equipment that contact raw materials, intermediates or APIs were made of materials that do not alter the quality of the intermediates and APIs beyond the established specifications. Production equipment were used within the qualified operating range. Major equipment (e.g. reactors, storage containers) and permanently installed with processing lines used during the production for an intermediate or API appropriately identified. Closed or contained equipment were used in both Unit I and Unit II. Where equipment was opened, a barrier was used as a precaution to minimize the risk of contamination. A set of current drawings was maintained for equipment and critical installations (e.g. instrumentation and utility systems).

Written procedures were established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Equipment and utensils were cleaned and stored in a manner that would prevent contamination or carry-over of a material that would alter the quality of the intermediate or API. Equipment assigned to campaign production of successive batches of the same intermediate or API, were cleaned at appropriate intervals to prevent build-up and carry-over of contaminants. Non-dedicated equipment were cleaned between production of different materials to prevent cross-contamination. Equipment was identified as to its content and its cleanliness status by inserting a status on a labelling board.

Control, weighing, measuring, monitoring and test equipment critical for assuring the quality of intermediates or APIs was calibrated according to written procedures and an established schedule. The current calibration status of critical equipment were indicated on a label placed on the equipment.

Computerized systems were used in the manufacture of APIs. These included a system for tracking deviations, CAPA and complaints using software known as “Trackwise”; a system for management of change requests and documents (Specifications and Corporate SOPs) known as “CIPDOX” and for laboratory operations, the LIMS system. The company was using SAP for materials management, generation of master Batch Manufacturing, Packing records and Vendor management system. At the time of the inspection, upgrading of the computerized system for operation of the reactors was being undertaken to reduce manual operations through installation of SCADA (EDLMS) for Data Acquisition from Process Equipment.

Computerized systems had sufficient controls to prevent unauthorized access or changes to data. There were controls to prevent omissions in data. There was record of when data changes were made, previous entry, the person who made the change and when the change was made. Written procedures were available for the operation and maintenance of computerized systems.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

5. Documentation and records

Documents related to the manufacture of API were prepared, reviewed, approved and distributed according to written procedures. Document control was the responsibility of QA. 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.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

6. Materials management

There were written procedures describing the receipt, labelling, quarantine, storage, and handling of materials, as well as the procedures for sampling, testing and approval or rejection of materials. No rejected materials were seen in the warehouse.

Qualification of vendors was performed according to SOP on Selection, evaluation and approval of manufacturer. The procedure provided instructions on approval of new and alternate manufacturers for APIs and intermediates and their requalification procedure.

All containers of API starting materials were 100% sampled whereas for other materials the formula square root (n) +1 was used.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

7. Production and in-process controls

Production processes were guided by documented procedures and instructions. Production processes including synthesis, purification, crystallization, drying, milling etc were conducted in a non-dedicated facilities and multi-purpose equipment to manufacture the APIs in focus of this inspection. Clean areas were available for the final steps of the API's manufacture, such as isolation, drying, milling, sifting, and packaging. There were in-process controls conducted at appropriate stages of the synthesis to monitor performance of the process and quality of the intermediates and APIs.

Production areas for Unit I and Unit II were inspected. Raw materials for manufacturing of intermediates and APIs were weighed under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices were of suitable accuracy for the intended use. Critical weighing operations were witnessed by a second person. Actual yields were compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges were established based on validation data. Deviations in yield associated with critical process steps were investigated to determine their impact or potential impact on the resulting quality of affected batches. Deviation were documented and investigated.

In-process sampling and controls written procedures were established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria were defined based on the information from validation studies. Critical in-process controls including the control points and methods, were stated in writing and approved by the quality assurance unit. All tests and results were documented as part of the batch record. Written procedures described the sampling methods for in-process materials, intermediates and APIs. Production operations were conducted in a manner that would prevent contamination of intermediates or APIs by other materials. Precautions to avoid contamination were taken especially after purification of the APIs.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

8. Packaging and identification labelling of APIs and intermediates

Packaging and identification labelling of APIs and intermediates was undertaken following a written procedure describing the receipt, identification, quarantine, sampling, examination, release and handling of packaging and labelling materials. Containers provided adequate protection against deterioration and contamination of the intermediate and API that could occur during transportation and recommended storage.

Documented procedures for label issuance and control were used to reconcile the quantities of labels issued, used and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued.

Packaging and labelling operations were carried out in areas separated from other operations involving other intermediates or APIs. Labels used on containers of intermediates or APIs indicated the name or identifying code, the batch number of the product and the storage conditions. Packaging and labelling facilities were inspected immediately before use to ensure that all materials not needed for the next packaging operation had been removed. This examination was documented in the batch packaging record.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

9. Storage and distribution

The company had separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs.

Handling and storage of materials was performed in a manner to prevent degradation, contamination and cross-contamination. Materials were stored in fibre drums, bags or boxes off the floor and suitably spaced to permit cleaning and inspection. Materials requiring cool storage like Artemisinin were stored in an area with controlled conditions (Temperature: 15-25ºC and Relative Humidity: NMT 75%). The record of the reading at the time of inspection was 19.5ºC and RH 51%.

Volatile materials were stored in a separate area outdoors. There was a separate area for storing rejected materials which were identified as such and controlled SAP software system designed to prevent their unauthorized use in manufacturing.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

10. Laboratory controls

The quality unit was independent of production. Documented procedures were in place for sampling, testing, approval or rejection of materials and recording and storage of laboratory data. Appropriate specifications for APIs were established in accordance with accepted standards.

Out of specification procedure (LIMS) was discussed. OOS consistently noted for related substance and assay test for certain products.

The SOP on analytical incidences investigation and resolution procedure was discussed. The procedure described the methodology as to how to report, investigate, evaluate and document analytical incidences causing non-conformance other than OOS and OOT. The procedure defined the term analytical incidences and provided examples such as, instrument malfunctioning, analyst error, variation of results among replicate determinations, abnormal response or pattern of standard or sample, system suitability failure or any kind of other error. The procedure provided process flow chart on the handling of incidences. Analytical incidences were handled through LIMS. The procedure required trending of analytical incidences once every three month.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Validation

In general, process validation was found satisfactory.

Validation and verification of analytical methods was discussed. Analytical methods were developed by the analytical development department (also sometime by the site) and validated by the site whereas verification was done on pharmacopoeial methods. Different characteristics were performed to validate and verify analytical methods. The acceptance criteria were based on pharmacopoeia and ICH guideline.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

12. Change control

A formal change control system was established to evaluate all changes that may affect the production and control of the intermediate or API. Changes were made in accordance with Change Control procedure. The change control procedure flow charts for corporate and API Manufacturing were reviewed and found to be satisfactory. Change requests were managed using CIPDOX software since July 2015.

The register of changes in 2015, 2016, 2017, 2018 were checked. Proposals for changes were reviewed and approved by the Quality Assurance units. The potential impact of the proposed change on the quality of the intermediate or API was evaluated. When implementing approved changes, measures were taken to ensure that all documents affected by the changes were revised.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Rejection and re-use of materials

There were established procedures for rejection, reprocessing, reworking of batches of intermediates and APIs during manufacture. According to the records provided there was no reworking for the APIs inspected.

There were established procedures for recovery of materials and solvents. Solvent recovery was used in the manufacturing process for the APIs inspected.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Complaints and recalls

The company had a procedure for handling complaints and recalls. According to the records provided there were no product complaints and recalls recorded.

This section was not covered in detail due to time constraint.

15. Contract manufacturers (including laboratories)

Cipla Patalganga uses two contracted laboratories for the testing of potable water from Bhabha Atomic Research Centre (for radioactive substances) and Geochem laboratory for chemical tests (Arsenic and other).

This section was not covered in detail due to time constraint.

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: Artemether, Artesunate, Lamivudine, Lumefantrine, Moxifloxacin, Daclatasvir Dihydrochloride manufactured at **Cipla Ltd, Unit 1, Plot A-33 & A-2** and **Unit 2, Plot A-42** MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, 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-sixth 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. Fiftieth 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. Fiftieth 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. Fiftieth 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. Fiftieth 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