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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**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-37/2/2 & A-2 MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, India Cipla, Unit 2, Plot A-42 MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, India
Unit / block / workshop number	Unit-I & II
Manufacturing license number, (delete if not applicable)	Unit-I : Form 26 - license No (25) 845 & (28) 707 valid until 31.12.2022 Unit 2: Form 26 - license No (25) KD620 & (28) KD 435 valid until 17.08.2021
Inspection details	
Dates of inspection	19 to 25 January 2018
Type of inspection	Routine GMP inspection with emphasis on the findings of the recent USFDA inspection of December 2017
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.

<table>
<tr><td></td><td>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 centers 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.

Formulation blocks are located on the plots as indicated below:

<table>
<tr><th>UNIT</th><th>Plot No.</th><th>Block</th></tr>
<tr><td>I</td><td>Plot No. A-33,
Plot No. A-2,
and
Plot No. A-37/2/2</td><td>Pharma</td></tr>
<tr><td>II</td><td>Plot No. A-42</td><td>Pharma</td></tr>
</table>
</td></tr>
<tr><td>History</td><td>Cipla Patalganga Formulation facility was last inspected by WHO PQ in February 2014. The site has also been inspected by several medicine regulatory authorities including MHRA UK, TGA Australia. Recently, the site was inspected by USFDA in November/December 2017.</td></tr>
<tr><td>Brief report of inspection activities undertaken</td><td></td></tr>
<tr><td>Scope and limitations</td><td></td></tr>
<tr><td>Areas inspected</td><td>The inspection covered the following sections of the WHO GMP Main Principles for non-sterile pharmaceutical products:
o Pharmaceutical quality system (Quality risk management and Product quality review)
o Good manufacturing practices for pharmaceutical products
o Sanitation and hygiene
o Qualification and validation
o Complaints and Recalls
o Personnel
o Training
o Personal hygiene
o Premises
o Equipment
o Materials
o Documentation
o Good practices in production
o Good practices in quality control</td></tr>
<tr><td>Restrictions</td><td>None</td></tr>
</table>

Out of scope	Only WHO products were covered during the inspection
WHO product numbers covered by the inspection	Pre-qualified Products manufactured in Unit I and Unit II 1. MA104 Artesunate and Amodiaquine as hydrochloride tablets 100mg/270mgMA103 Artesunate and Amodiaquine as hydrochloride tablets 50/135mg 3. MA102 Artesunate and Amodiaquine as hydrochloride tablets 25mg/67.5mg 4. HA488 Abacavir (as sulfate) dispersible tablets 60mg 5. HA371 Abacavir (as sulfate) tablets 300mg 6. HA518 Abacavir (as sulfate) and Lamivudine dispersible tablets 60mg/30mg 7. MA064 Artemether and Lumefantrine tablets 20mg/120mg 8. TB210 Moxifloxacin (as hydrochloride) tablets 400mg 9. HA511 Nevirapine dispersible tablets 100mg 10. HA510 Nevirapine dispersible tablets 50mg 11. TB225 Ofloxacin tablets 400mg 12. TB224 Ofloxacin tablets 200mg 13. MA079 Artesunate and Mefloquine (as hydrochloride) tablets 100/200mg 14. MA078 Artesunate and Mefloquine (as hydrochloride) tablets 25/50mg 15. TB215 Ethionamide tablets 250mg <u>Pre-qualified products manufactured in Unit I</u> 1. HA662 Abacavir (as sulfate) and Lamivudine dispersible tablets 120mg/60mg 2. HA369 Isoniazid, Pyridoxine hydrochloride, Sulfamethoxazole & Trimethoprim tablets 300/25/800/160mg <u>Pre- qualified products manufactured in Unit II</u> 1. HP004 Sofosbuvir tablets 400mg 2. HA627 Darunavir Ethanolate tablets 400mg 3. HA628 Darunavir Ethanolate tablets 600mg 4. HA632 Atazanavir (as sulfate)/Ritonavir tablets 300mg/100mg 5. HA666 Lamivudine and Tenofovir Disoproxil Fumarate tablets 300mg/300mg 6. HA593 Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate tablets 600mg/300mg/300mg <u>Product under registration manufactured in Unit II</u> 1. HA664 Darunavir Ethanolate tablets 800mg 2. HA628 Darunavir Ethanolate tablets 600mg

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**

1. Pharmaceutical quality system

The implementation of the pharmaceutical quality system (PQS) at the facility level was reviewed and found robust. The global procedures in place were for handling complaints, notice of rejection, handling incident and laboratory investigation reports, corrective/preventive actions (CAPA) with effectiveness checks, for reporting of analytical results and for preparing issuance of technical (quality) agreements. There was extensive use of computerized systems for deviation management, CAPA, change control, complaints, testing, reporting of quality control results and training and they were all validated and under control. The following software systems were in place: Trackwise, LIMS, Chromeleon, SAP, Cipdox and LMS. Incidence and complaints were adequately investigated and trended periodically. The quality system was adequately resourced with experienced and trained personnel.

Quality Risk Management (QRM)
Risk management by failure mode, effects and criticality analysis was reviewed. The procedure was applicable to different aspects of pharmaceutical quality like development, manufacturing, testing, distribution, inspection and submission / review processes throughout the lifecycle of the drug substance, drug products including equipment, facilities, system, raw materials, solvents, packaging, labelling and manufacturing operations which are likely to affect the product or process and any other activity which is directly or indirectly affecting product quality.

Management review (MR)
MR was in place.

Deviations and corrective and preventive actions (CAPA)
Deviations and CAPA procedures were available.

Change control
CC procedure was available.

Product Quality Review (PQR)

Product Quality Review was undertaken on a rolling basis for all pharmaceutical products with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to identify product and process improvements. Product quality reviews for selected products were examined to assess whether the manufacturer had documented and evaluated the reviews appropriately.

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

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were implemented and followed. Required staff and system resources were provided. Manufacturing processes were clearly defined and documented. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and comprehensive records were made during manufacture. Some minor deficiencies were noted.

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

3. Sanitation and hygiene

In general, premises and equipment were maintained at a satisfactory level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility, with appropriate changing rooms.

4. Qualification and validation

The company approach to validation was documented and explained in the Validation Mater Plan (VMP) and the VMP was briefly reviewed by the inspectors. The key elements of a qualification and validation programme were defined.

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

5. Complaints

The SOP on the handling of product complaint was reviewed. This is a corporate procedure which is common for the drug substances and drug products. The SOP provided a procedure for recording and investigating any product or medical device complaints received from the customers (local and export). All complaints are received at the corporate before being transferred to respective sites. In case, if site receives the complaints, the same is forwarded to the corporate for logging. The complaints were categorized as technical and medical complaints. The complaints related to medical were handled by the corporate safety department. The procedure was cross referenced to Risk Management Procedure. The procedure provided a matrix for product complaint investigation.

There were no issues related to complaint area.

6. Product recalls

There were few product recalls registered related to non WHO registered products.

7. Contract production, analysis and other activities

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

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

Self-inspection was carried out following the corporate procedure. The procedure provided instructions on Evaluation and certification of inspectors; Composition of the audit team; Planning and scheduling internal audit; Inspection for non- routine unscheduled inspections to check on specific system or area.

Quality audits were performed in accordance with a vendor audit management programme which was found satisfactory. Some active pharmaceutical ingredients were manufactured at the Cipla API facility in the same location as the formulation facility while other raw materials were sourced from approved external sources.

9. Personnel

Sufficient qualified personnel were employed to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities were clearly defined and understood by the persons concerned and recorded in written job descriptions. Reporting relationships were clearly specified in the organization chart. The organogram for both Unit I and Unit II were checked which revealed independent reporting relationship between production and QA/QC units.

10. Training

The manufacturer provided training in accordance with a written Corporate SOP no. 1035-G-0006 for all personnel whose duties take them into manufacturing areas or into Quality control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required. Basic training on the theory and practice of GMP was given to newly recruited personnel and also training appropriate to the duties assigned to them. Continuing training was given, and practical effectiveness assessed. Training records for two analysts were checked.

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

11. Personal hygiene

Changing and washing before entry to production areas followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. The approach to sanitation and hygiene was in general acceptable; during the inspection in the production areas, personnel wore adequate clothes related to the activities to be performed.

12. Premises

The facility (Unit-I & Unit-II) was designed in a unidirectional flow with epoxy floored floors and the walls were painted with polyurethane paint. The facility was fitted with separate air handling units for clean corridors, maintained overpressure respect to the production rooms, and for each processing area and the same were interlocked in case of fan failure for air handling units supplying the clean corridor.

Rest and refreshment rooms were separate from manufacturing and control areas. Facilities for changing and storing clothes and for washing and toilet purposes were found clean and appropriate for the number of users. Toilets did not communicate directly with production or storage areas.

Storage areas were of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected products. Storage areas were designed or adapted to ensure good storage conditions. In particular, they were found clean, dry, sufficiently lit and maintained within acceptable temperature limits. There was a separate area for sampling starting materials and printed packing materials within the storage areas.

Production areas were effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas were regularly monitored during both production and non-production periods to ensure compliance with their design specifications. Premises for the packaging of pharmaceutical products were specifically designed and laid out so as to avoid mix ups, contamination or cross-contamination.

Quality Control laboratories for Unit I and Unit II were separated from production areas. The Microbiology section of the laboratory was also segregated from the rest of the laboratory area. QC laboratories were designed with sufficient space to avoid mix ups and cross-contamination. There was adequate suitable storage space for samples, reference standards including those with cooling), solvents, reagents and records. The design of the laboratories was made in such a way to prevent fumes. Separate air-handling units were provided to the microbiological laboratories. There were separate instruments room to protect them against electrical interference, vibration, and contact with excessive moisture.

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

13. Equipment

Equipment were located, designed, constructed, adapted and maintained to suit the operations to be carried out. Equipment were installed in such a way as to minimize any risk of error or of contamination. Fixed pipework were clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated according to a fixed schedule. Production equipment were thoroughly cleaned according to a fixed schedule. Laboratory equipment and instruments were suited to the testing procedures undertaken.

The parts of the production equipment that come into contact with the product were not reactive, additive, or absorptive to an extent that would affect the quality of the product. Defective equipment in the QC areas were clearly labelled as defective to prevent use. Current drawings of critical equipment and support systems were maintained.

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

14. Materials

All incoming materials and finished products were quarantined immediately after receipt or processing, until they were released for use or distribution. Materials and products were stored under the appropriate conditions established by the manufacturer, and in an orderly fashion, to permit batch segregation and stock rotation by a first-expire, first-out rule. Purified water and portable water was used at various stages of the manufacture of pharmaceutical products. Food grade oil was used for lubrication of punches and dies.

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

15. Documentation

Documents were designed, prepared, reviewed and distributed in accordance with corporate procedure and documentation control. They were approved, signed and dated by the appropriate responsible persons. No document was changed without authorization and approval. Documents were regularly reviewed and kept up to date; SOPs were reviewed every three years.

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

16. Good practices in production

The manufacturing premise was in a good state of repair. There were adequate gowning procedures in place. There were dedicated places for storage of in-process materials, granulation areas, blending areas, compression areas, coating areas, tablet inspection areas, in-process control areas, washing areas and packaging areas. Tableting rooms had provisions for in-process monitoring of all parameters except for the disintegration and friability tests which were carried out the in-process control laboratory by IPQA personnel. There were detailed procedures for line clearance, cleaning and operating machines. There was a robust process for verification of dispensed material when they were received and issued out of the storage areas.

The pressure differentials and manufacturing conditions were all with limits.

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

17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that the QC arrangements are effectively and reliably carried out in general.

The movement of samples and analysis was being traced through the Laboratory Information Management System (LIMS) and all HPLC were connected using Chromeleon software. All the systems were validated with audit trail functionality. The laboratory was equipped with adequate modern instruments that were regularly qualified. There were adequate personnel who were qualified for the quality control various activities carried out by the manufacturer. There were separate quality control facilities for routine testing and for stability and validation studies.

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

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, *Cipla Ltd located at Unit 1, Plot A-33, A-37/2/2 & A-2 and Unit 2, Plot A-42 MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, India* was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

PART 4
List of GMP guidelines referenced in the inspection

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

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

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-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