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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Cipla Limited.
Corporate address of manufacturer	Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra 400 013 India
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Cipla Ltd. (Baddi Site) P.O. Bhud, Upper Malpur Village, Tehsil, Nalagarh, Solan District, Himachal Pradesh, 173 205, India
Unit / block / workshop number	Unit I
Inspection details	
Dates of inspection	29 January – 2 February 2024
Type of inspection	Routine inspection
Introduction	
Brief description of the manufacturing activities	Production and quality control of OSDs, metered dose inhalers (MDIs), and dried powder inhalers (DPIs)
General information about the company and site	Cipla Ltd. is a public limited company established in 1935. The Baddi site is a formulation manufacturing site comprising of Unit I and Unit II. At Cipla Baddi, Unit I, several dosage forms were manufactured, such as uncoated and film-coated tablets, hard gelatine capsules, MDIs and DPIs. Unit II has a dedicated warehouse and QC facilities and produces pellets and capsules. According to the information provided by the company, no hormones, penicillins,, or cephalosporins were manufactured at the Cipla Baddi plant. No production of WHO prequalified products was planned during the course of the inspection for commercial reasons (no orders). Some other products were produced on the same production line at the time of this inspection.
History	The site was subject to two WHO onsite inspections in 2012 and 2016, and a desk assessment in 2020. Furthermore, the site was inspected by TGA, Australia remotely in October 2021, and is regularly inspected by CDSCO, India.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	• Quality management system • Production block: Unit 1 - Material dispensing - Tablets

	- Filmcoated tablets - Primary and secondary packaging • QC laboratories including physicochemical and microbiological laboratories • Warehouses • HVAC system • Water system • Compressed air
Restrictions	The scope of the inspection was restricted to the FPPs in the WHO PQ programme.
Out of scope	Products which are not under the scope of prequalification.
WHO products numbers covered by the inspection	HA060 Lamivudine/Zidovudine 150mg/300mg Tablet, Film-coated MA064 Artemether/Lumefantrine 20mg/120mg Tablet MA122 Artemether/Lumefantrine 80mg/480mg Tablet
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BMS	Building management system
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory

MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Nonconformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments**

1. Pharmaceutical quality system

The principles of the PQS were adequately described in the Quality Manual. A documented system for quality assurance at corporate level was established, with procedures covering key quality elements in place. The Quality Department including QA and QC was separate from the Production Department. Operations were specified in written form and critical GMP requirements were met.

Product Quality Review (PQR)

The SOP for product quality review (PQR) for WHO registration was made available. The SOP provided for the preparation of APQR within a specified timeframe from the end of the reporting period. In addition, the SOP mandated preparation of an APQR even if batches were not manufactured during the review period and stability study of the product was ongoing. Furthermore, the SOP provided for the preparation of an APQR as long as marketing authorization was valid even if no batches were produced.

As no recent batches were produced for Artemether/Lumefantrine or Lamivudine/Zidovudine were manufactured in past three years, the APQR of a frequently produced product on same production line was reviewed.

Quality Risk Management

The SOP "Risk management by failure mode, effects and criticality analysis" was reviewed and discussed. The procedure described the Failure Mode Effects Analysis (FMEA) with RPN acceptance criteria. Few examples of risk assessment performed for OSD production operation were discussed.

Management Review (MR)

The SOP "Quality management review (QMR)" was checked. The MR was reviewed at site level and corporate level. KPIs were used for performance evaluation of the QMS and production. A MR meeting held in 2023 was checked and found to be satisfactory.

Deviations

There was a procedure in place defining the principles for initiating, recording, investigating deviations, and applying appropriate CAPA. QA was responsible for putting together a team to investigate the deviation followed by CAPA and closing the deviation as appropriate. The list of deviations related to tablet finished products in 2023 was reviewed.

Change control

A procedure for change management was in place and described the details for initiation, approval, action plan and closure of a change. At the time of the inspection, changes were managed with a computerized system. The list of changes in 2023 and several changes implemented in 2023 were reviewed.

Product Release

The SOP "batch release system of formulation" was checked. The final batch review was performed using check list by QA and batches were released using the SAP system.

Data integrity management

The SOP "Backup and restoration of electronic data in server and end point system" was checked. QA was responsible for data integration management and review of the audit trail in the computerized systems. The responsibility of data backup and restoration was specified. The production data and the audit trial of a tablet product was discussed.

2. Good manufacturing practices for pharmaceutical products

Manufacturing processes were clearly defined and systematically reviewed. Qualifications, validations, calibrations and maintenance were performed according to prepared protocols and followed the relevant established procedures. Manufacturing steps were recorded in batch manufacturing and packaging records. BMRs and BPRs were made available during the tour of the facilities. The necessary resources including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, approved procedures, and instructions were provided for the current operational level of manufacturing and testing.

It was noted that there have been no commercial batches of WHO prequalified products produced and supplied to the market from this site in the past three years.

3. Sanitation and hygiene

Premises and equipment were maintained at a satisfactory level of cleanliness at the time of inspection. At Unit I, there was appropriate gowning procedure. The company had procedures in place for personal health and hygiene. Health records were spot-checked during the inspection.

Areas were cleaned in accordance with an approved written program and SOPs. Microbial monitoring was regularly performed as per SOP for microbiological monitoring of environment, surfaces and personnel along with SOP for trend analysis. Similarly, the trending of EM data of blending and packaging area for the period 2021 – 2023 were reviewed. In addition, SOP for uniforms including procurement and washing was reviewed along with quality agreements for laundry service provider.

4. Qualification and validation

The validation master plan was available covering all GMP qualification and validation activities. The document described the overall philosophy and strategy of the company towards validation and qualification including but not limited to, scope, plan, activities, frequency, and responsibilities as well as relevant templates and records. Additionally, the SOP related to corporate technical guideline on product assessment/validation protocol and report were reviewed. The latter documents mandated that validation batches released to the market only after successful PV.

Since the WHO prequalified, products were not produced at the site over a relatively long period, emphasis was made on the company's policy for revalidation and periodic verification. As a matter of fact, the manufacturing process of Lamivudine/Zidovudine was never validated since registration batches were only produced on-site in 2010.

The SOP for execution of registration and assessment batches was also reviewed noting that these batch or batches are not validated and cannot be released to the market. Rather, these batches were produced for the sole purpose of serving regulatory submissions.

Process Validation

The SOP for process validation was reviewed. Several documents were reviewed with respect to PV of WHO prequalified products which were performed more than five years ago.

On the other hand, for Lamivudine/Zidovudine, three registration/assessment batches were produced in 2010. PV was never executed for this product at the Cipla Baddi site. As per the respective policies and procedures, should this product be produced at the Cipla Baddi site, PV will have to be completed before product release.

Cleaning Validation(CV)

The SOP for cleaning validation and related documents for the determination of Permitted Daily Exposure (PDE) values governing cleaning validation activities at the manufacturing facility were checked. For any newly introduced product, a cleaning verification exercise would be performed. Several documents were reviewed with respect to cleaning validation activities including equipment CV protocol and reports, as well as the relevant risk assessments.

Equipment qualification

The SOP for equipment qualification was reviewed. Sample reports of qualification of critical equipment were spot-checked. In addition, the SOP for preventive maintenance along with the preventive maintenance schedule were reviewed.

Computerized system validation (CSV)

Several computerized systems were utilized in the production and quality control of medicines at Cipla Baddi site. The qualification and validation were executed as per the respective policies and procedures including provisions indicated in the VMP and SOP for CSV. Sample CSV and periodic revalidation were spot-checked.

HVAC system

The HVAC system located in Unit I production building was briefly visited. The SOP for qualification of production areas and the HVAC system along with guidance for the preparation of qualification and verification documents were reviewed. The frequency of requalification met WHO guidelines for class D areas. In addition, documents were reviewed with respect to regular requalification of production areas of relevance to WHO prequalified products. Furthermore, a risk assessment of the HVAC system and layout covering potential risks of failure were reviewed.

Water system

Borewell water was collected and pre-treated. The PW system in the Unit I production building was briefly visited. The PW was produced by Reverse Osmosis (RO) followed by Electro-deionization (EDI) with one generation system and two distribution loops at ambient temperature. Piping and Instrumentation Diagram (P & ID) of the water system was available. Stainless steel 316L was utilized for pipes and vessels.

The SOP "Operation, cleaning and sanitization of water generation system" and SOP "Operation, sanitization and alarm monitoring procedure" were checked. The sanitization was regularly performed for PW storge and distribution loop. The flow velocity, conductivity, TOC and pH were monitored on-line. The annual review of purified water system from January to December 2023 was checked and discussed.

5. Complaints

The SOP for complaints handling was reviewed along with list of complaints in 2023 and 2022. The SOP provided for recording of all the original details of the received complaint and thorough investigation of the same by a multi-functional team led by QA department. In the event of verification of the complaint, root cause investigation was performed with attempt to identify the root cause (or the most probable one/ones) followed by remedial, corrective and preventive actions as appropriate. Several example complaints were spot-checked; proper investigations were performed and CAPA addressed the identified root causes based on the investigation.

6. Product recalls

The SOP for products recall was reviewed. The qualified person was responsible for recall activities. No recalls were needed or executed in 2022 or 2023. The aforementioned SOP provided for mock recall on annual basis with clear criteria for selection of products and batches for mock recall. Records of the mock recalls were checked and found to be compliant with the relevant procedure.

7. Contract production, analysis, and other activities

The production of the WHO prequalified FPPs covered within the inspection scope was not sub-contracted.
The testing for Nitrosamine impurities was subcontracted to an external contract testing laboratory. The quality agreement for contract testing was spot-checked. The Analytical method validation for impurity testing signed by the contract lab and approved by Cipla was checked.

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

A procedure for the evaluation and qualification of suppliers was in place. The SOP provided for proper qualification of the suppliers prior to actual supply and purchase of the concerned services and products including provisions for a quality questionnaire or onsite audits, if necessary. Approved suppliers were also subject to regular audits, if needed, based on quality risk management. The supplier qualification of an Indian based API manufacturer as well as the laundry service provider for the gowns were spot checked.

A procedure for internal audit was in place. The internal audit programme was managed at the corporate level. The audit schedule for 2023 was reviewed.

9. Personnel

The procedure for organizational chart and job responsibilities guiding establishment of the organization structure was reviewed. The organization of the manufacturing (production) activities was separate from the quality activities with dedicated supervisory and reporting pathway. Several job descriptions were spot-checked.

10. Training

A procedure for training was reviewed along with training schedules for 2023 and 2024. Sample training activities were spot-checked. Assessing the effectiveness of trainings was an integral part of the training programme including provisions for post-training questionnaire and performance evaluation.

11. Personal hygiene

The procedure for personnel health and hygiene was reviewed and found to be appropriate. All staff working at the site are subject to annual medical examination with the exception of visual inspectors who undergo semi-annual eye check in order to keep them qualified for their work activities.

12. Premises

There are two Units at Cipla Baddi site. Unit I was relevant and covered during this inspection considering the fact that WHO prequalified products were authorized to be produced at this unit. Layouts of the facilities were made available. In general, premises were constructed, designed and maintained to suit the operations to be carried out and prevent the risk of contamination of materials and products. Several documents were reviewed with respect to design, operation and control of the premises and utilities.

13. Equipment

Production equipment was of good standard and appeared to be well maintained. Spot-checks on production balances and differential pressure gauges indicated that equipment and devices were calibrated timely. The workflow in the facility was appropriately designed, and the equipment appeared to be installed to facilitate production and reduce the risk of contamination and mix-ups. In general,

most production equipment was identified as to its content or purpose with cleanliness status identified by appropriate labels. A procedure for the preventive maintenance was in place.

Some changes had been introduced to the equipment used for the production of WHO products. This included relocation of the granulator. In addition, several other equipment were changed including the fluid bed dryer, vibratory sifters, and multi-mills.

14. Materials

Materials were controlled and managed according to a well-established set of procedures including an SOP for sampling APIs and packaging materials; an SOP for receipt, registration and testing of samples and an SOP for dispensing APIs and excipients to the production area. These procedures were reviewed and adherence to the same was spot-checked during the tour within the warehouse.

Rejections

The SOP "Handling of rejected material and its disposal" and the SOP "Scrap handling and disposal operation" were checked. The procedures were applied to manufacturing and packaging of drug substance and drug products.

15. Documentation

Documents were designed, prepared, reviewed and distributed in accordance with the relevant procedure for document control. Documents were approved, signed and dated and had unambiguous contents. The procedure covered all quality documents except for validation documents which were governed by a different procedure. Procedures were reviewed on regular basis. QA was responsible for monitoring the periodic review of the SOPs and associated documents and would identify documents to be reviewed prior to their review due date. Several key documents were spot-checked including:

- Quality manual
- CAPA management
- Example of CAPAs

Batch numbering system and BMR/BPR management

The SOP "Batch numbering system for inward and materials produced inhouse (Formulation)" was checked. Reprocessing and reworking were indicated in batch number. The procedure for generation, approval and issuance of master batch document, batch record and handling of excess material was reviewed. Master Manufacturing Formula for artemether/lumefantrine tablets and example BMRs were checked and discussed.

16. Good practices in production

Production operations followed clearly defined procedures in accordance with manufacturing and marketing authorizations. Deviations from procedures were recorded and investigated. During processing materials, bulk containers, major items of equipment, rooms and packaging lines being used, were labelled with product or material being processed, its strength and the batch number. Access to production premises was restricted to authorized personnel. In-process controls were performed within the production area.

Inspectors toured the different production areas including incoming materials warehouse (receipt, quarantine, release, rejected, sampling and dispensing areas); finished good warehouse; as well as production areas (sifting, granulation, drying, blending, intermittent storage, compression, blistering

and secondary packaging areas). No WHO products were produced during the inspection, but other products were manufactured at the same production suites.

Entrance to the production floor was via change rooms. Relevant SOPs and photos of entry procedure were on display. Entry and exit procedures to compression cubicles and contamination control were discussed. Temperature and relative humidity T&RH along with pressure differentials were manually recorded. The BMS system for T&RH was under qualification.

Main production equipment such as the granulators, compression machines, coating pans were supported with, and processes were controlled by PLCs. Access to PLCs was password protected. Production parameters were set for each product in the PLCs. Metal detectors were available and checks were performed before and after compression by using three types of standards. Product specific punches and dies were properly stored and their use including regular cleaning was ensured and recorded in the respective register.

The packaging production area was briefly visited and spot-checked. The SOP "Handling and utilization of rejections and controls" was checked.

17. Good practices in quality control

The QC function was independent of other departments. The site had two QC labs belonging to Unit 1 and Unit 2 respectively. The physicochemical laboratory was briefly visited. The microbiology laboratory was segregated from the chemistry laboratory. A Laboratory Information Management System (LIMS) was employed in the QC lab for testing and reporting of testing results.

Sample receiving and distribution

An access-controlled cabinet for sample receipt was available. The sample register and the information for receiving and distribution were checked. The traceability of raw data was available in the sampling records.

Testing of starting materials and finished products

Testing of starting materials and finished products were performed according to specifications and standard testing procedures. The SOP "Certificate of analysis" was checked and discussed. The CoA templates were established and controlled at the corporate level. In addition, the offline CoAs were also allowed to be prepared and edited.

PW used in the QC lab was prepared by a Milli Q system. The operation and monitoring of the Millipore water system equipment was spot-checked.

OOS/OOT management

SOP "OOS and OOT investigation procedure" and SOP "Investigation of aberrations in Microbiological test results" were checked. The flow charts for OOS and OOT investigation were acceptable. The microbiological OOS investigation was discussed. The OOS/OOT results were managed in the LIMS system. OOS/OOT results were reported and reviewed in the management review meeting.

Retention samples

Retention samples were kept in a secured and temperature-controlled (15 ^{0}C – 25 ^{0}C) room for each dispatched batch of finished goods. The retention samples were registered and monitored in the LIMS system with the retention time clearly defined.

Stability study

The stability study chamber located outside of Unit 1 was spot-checked. A range of stability chambers were available for different condition including 30 ^{0}C with RH 75%, 30 ^{0}C with RH 65%, 25 ^{0}C with RH 60% and 2 – 8 ^{0}C.

The WHO PQ products have not been produced for relatively long period of time and was no ongoing stability due to the lack of production.

Instrumentation

The company has adequate number of instruments and equipment for QC laboratories. Records and logs were maintained. Status labels were attached to equipment and found acceptable. Calibration status and validity were acceptable. QC chromatographic analysis with 25 HPLCs and 3 GCs were operated and controlled with Chromeleon software with real time transfer.

Microbiology Laboratory

Microbiological testing activities were executed following well established procedures. Several documents were reviewed in relation to production activities including:

- Validation of the Autoclave used for sterilization of the media, garment and accessories at the microbiological lab.
- Growth promotion test (GPT) qualification report.

Part 3	**Conclusion – Inspection outcome**

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 Baddi site (unit I)***, located at***, PO Bhud, Upper Malpur Village, Solan District Tehsil, Nalagarh, Himachal Pradesh 173 205 India*** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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

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

Part 4	**List of GMP Guidelines referenced in the inspection report**

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
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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. ***Short name: WHO TRS No. 957, Annex 2***
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3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
Short name: WHO TRS No. 1033, Annex 3
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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.
Short name: WHO TRS No. 929, Annex 4
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5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1010-annex8-who-gmp-heating-ventilation-airconditioning.pdf?sfvrsn=c77698e2_0

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.
Short name: WHO TRS No. 937, Annex 4
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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.
Short name: WHO TRS No. 961, 957), Annex 1
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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 3.
Short name: WHO TRS No. 957, Annex 3
https://digicollections.net/medicinedocs/documents/s22358en/s22358en.pdf

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.
Short name: WHO TRS No. 961, Annex 6
https://digicollections.net/medicinedocs/documents/s19959en/s19959en.pdf

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7.
Short name: WHO TRS No. 961, Annex 7
https://digicollections.net/medicinedocs/documents/s18677en/s18677en.pdf

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. ***Short name: WHO TRS No. 961, Annex 9***
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12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3***
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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.
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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.
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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.
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Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***

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

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. ***Short name: WHO TRS No. 992, Annex 5*** Essential Medicines and Health Products Information Portal (digicollections.net)

20. WHO Recommendations for quality requirements when plant – derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
https://www.who.int/publications/m/item/who-recommendations-for-quality-requirements-when-plant-derived-artemisinin-is-used-as-a-starting-material-in-the-production-of-antimalarial-active-pharmaceutical-ingredients---trs-992---annex-6

21. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS No. 1033, Annex 4***
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22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
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24. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
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25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. **Short name: WHO TRS No. 1033, Annex 2**
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26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. **Short name: WHO TRS No. 1025, Annex 6**
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27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***
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28. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. ***Short name: WHO TRS No. 1025, Annex 4***
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