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Prequalification Team Inspection Services
WHO Public Inspection Report (WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Cipla Quality Chemical Industries Ltd. (CiplaQCIL)
Corporate address of manufacturer	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai: 400013, India
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Plot No 1-7, 1st Ring Road, Luzira Industrial Park, PO Box 34871, Kampala Uganda
Unit / block / workshop number	Main building
Inspection details	
Dates of inspection	19 to 22 September 2022
Type of inspection	Routine re-inspection
Introduction	
Brief description of the manufacturing activities	Production, quality control and release of oral solid dosage forms, uncoated and coated tablets, as well as hard-gelatin capsules.
General information about the company and site	Cipla Quality Chemicals Industries Limited (CiplaQCIL) was founded in 2005 as a joint venture between QCL, a local regional manufacturer and major distributor and Cipla, India. The site was located at the Luzira Industrial Park about 2km from Luzira and about 10km from Kampala, Uganda. The manufacturing activities covered non-sterile oral solid dosage forms including coated tablets, non-coated tablets, hard-gelatin capsules in different therapy fields as anti-retroviral, anti-helminthic, vaso dilatator, anti-malarial, antiviral, anti-diabetic, anti-pyretic/anti-inflammatory, antibacterial. Apart from the manufacturing, the site has physico-chemical and microbiology laboratories for the testing of raw materials, intermediates, stability samples, water and environmental samples.
History	The site was previously inspected by WHO in December 2015 and June 2019.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	– Quality management system – Main Building, including: • Warehouses • Production facilities • Quality Control • Utilities, AHU • Water system
Restrictions	The inspection restricted on the products listed in the inspection scope.
Out of scope	Capsule manufacturing
WHO products numbers covered by the inspection	1. HA593 Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 600mg/300mg/300mg 2. HA702 Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 50mg/300mg/300mg 3. HA666 Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 300mg/300mg 4. HA639 Isoniazid/Pyridoxinehydrochloride/Sulfamethoxazole/ Trimethoprim Tablet 300mg/25mg/800mg/160mg 5. HA352 Efavirenz Tablet, Film-coated 600mg 6. HA060 Lamivudine/Zidovudine Tablet, Film-coated 150mg/300mg 7. MA064 Artemether/Lumefantrine Tablet 20mg/120mg 8. HA770 Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 400mg/300mg/300mg
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
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	Non conformity
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

A documented system for quality assurance was established, with procedures covering key quality elements in place. Operations were specified in written form and critical GMP requirements were essentially being met. The procedures reviewed and discussed during the inspection were generally of an acceptable standard.

Annual product Quality Reviews (APQRs)

The APQRs and the scheduler for the year 2020-2021 and 2021-2022 were prepared and available.

The following APQRs were reviewed and discussed in detail.

- APQR/21-22/ Artemether/Lumefantrine Tablet 20mg/120mg
- APQR/21-22/ Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 300mg/300mg
- APQR/20-21/Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 600mg/300mg/300mg
- APQR/20-21/Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 50mg/300mg/300mg.

Some observations noted during the inspection listed in the full report regarding APQRs were addressed by the manufacturer to an acceptable level.

Management review (MR)

Quality management review was managed according to the SOPs for MR. Management review was performed quarterly. The minutes of MR meeting held in July 2022 was reviewed during the inspection.

Quality Risk Management

Quality risk management and risk assessment was handled and performed according to the SOP for Risk management by failure mode, effects, and criticality analysis. The informal qualitative risk assessment was managed with a separate procedure which covered a procedure for investigation. An annual plan for risk assessment was available. The risk evaluation of processing Lamivudine 150mg/Zidovudine 300mg tablets scheduled for May 2022 was reviewed and was found generally acceptable.

Change control

Change control was managed according to the SOP for change control. Changes were categorized in major, moderate, minor. The change logbook for year 2021-2022 was available. Several major changes occurred at the company since the last inspection, e.g., expansion and relocation of QC laboratory, addition of new warehouse, addition of new granulation, coating, and spare and in-process storage area etc.

Deviations management

Deviations were handled according to the SOP for deviation and the SOP for investigation and root-cause analysis. Deviations were classified as critical, major & minor. The risk matrix was used for assessment. There were several major deviations recorded at the time of inspection. The record was managed by using Track Wise software®.

Product release

The finished products can only be distributed after the formal batch release according to the SOP for batch release for formulations. Upon the release, the status of the product was changed together with the generation of the following documents:

- Batch Release Certificate,
- Product Release Report Form
- Certificate of Analysis

The batch release of one Artemether/Lumefantrine Tablet 20mg/120mg batch was reviewed and discussed.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were generally implemented. Necessary human and physical resources with premises, equipment and utilities were provided for the current operational level of the tablet products manufacturing activities. The manufacturing processes followed procedures as defined and documented in the BMRs.

3. Sanitation and hygiene

Premises and equipment in the FPP production area were maintained at a satisfactory level of cleanliness at the time of inspection. Sanitation of clean areas is performed frequently in accordance with the SOP. Personal hygiene and sanitation appeared satisfactory. The facilities for sanitation and hygiene established on the site appeared acceptable.

The cleaning procedures for environment and for the equipment were in place. The cleaning and sanitation procedures focusing on the granulation room and the compactor were reviewed and discussed. The area cleaning and sanitization procedure was detailed in the written document including the cleaning agents to be used.

4. Qualification and validation

Validations and qualifications were performed according to the site policy, validation master plan, and documented procedures. Process validation and equipment qualification identified what qualification and validation activities were required. The key elements of a qualification and validation programme were defined. Validation Master Plan defined the criteria for revalidation including major changes to manufacturing processes, change in equipment or materials. The main principles of the validation qualification together with the planners were summarized in the VMP and the attachments.

There were different lists and schedules prepared for the qualification, calibration and for the related jobs performed by external party. Several equipment qualification/calibration records checked were available.

Process Validation (PV)

Process validation was performed according to the SOP for PV. The process validation protocol, report and three PV batches of Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 50mg/300mg/300mg were reviewed. Some observations noted during the inspection listed in the full report regarding process validation were addressed by the manufacturer to an acceptable level.

Cleaning validation

The main principles of the cleaning validation together with the cleaning validation schedule was available in the VMP and the annexes. Following to the initial validation of the cleaning process, periodic verification was scheduled for worst case scenarios.

The equipment used for manufacturing of products containing the active substance Lamivudine, Zidovudine and Tenofovir was checked. Accordingly, the limits for active and detergent residuals after cleaning were determined based on specified criteria.

The cleaning method together with the cleaning validation sampling plan (including rinse and swab sampling) was based on a detailed evaluation.

Computerized systems validation

There were computerized systems used for different functions including operating production and quality control equipment, data acquisition, etc. The proper functioning of the computerized system was assured by validation.

The validation documents of the software used for the stability and cold chambers were checked and discussed. The validation certificate was issued upon the validation plan. The assess to the system including user groups, user and user privileges were controlled by user management policy.

5. Complaints

The complaints were handled according to the procedure and flowchart. The complaints and the corresponding investigations were recorded in Track Wise software.

The deadline of the actions during the investigation including recording, acknowledgement, preliminary investigation, closure was defined. The complaints recorded in 2021 and in 2022 were reviewed and discussed.

6. Product recalls

The product recall procedure did not change since the last WHO inspection. The performance of the recall procedure is tested every 2nd year. The last was in November 2021. The case was closed as compliant. One recall initiated in 2019 was reviewed during the inspection.

7. Contract production, analysis and other activities

There was no contract production undertaken or contracted out. Contract laboratories were listed in the SMF.

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

The internal audit program was documented as defined by the procedure. The last audit performed at the manufacturing/packaging section held in March 2022 was checked. The audit report was prepared and responded by the audited department. The audit was already closed.

The suppliers of raw materials (including packaging materials, excipients, APIs) and the service providers (such as contract laboratories) were qualified. The requalification due time for vendors of APIs and for excipients were specified. Only the local vendors (in practice only secondary packaging materials) were qualified by the site. The rest of the vendors were qualified by the Corporate according to the SOP.

The qualification records of supplier for Lamivudine active substance and the laboratory for testing finished products for elemental impurities were reviewed and discussed during the inspection. The technical agreement containing the concerned analytical testing was available.

9. Personnel

The organizational charts reflecting the organizations, the positions and the reporting lines of the quality assurance, production, quality control, maintenance organizations were available. The quality assurance/quality control functions were independent from the production. The total number of the staff was 322 at the time of this inspection. The personnel had job descriptions. The job description of a department assistant (production) was discussed.

10. Training

The training program included the factory induction training, on-job trainings in the form of scheduled and un-scheduled trainings. The training program was supported and documented by the help of Learning Management System (LMS) software.

11. Personal hygiene

Personnel entering the production, packaging, warehousing, and quality control facilities had to wear company uniform. The changing rules were defined in SOP containing pictural guides of the process. The change-rooms entering the controlled areas were maintained as appropriate to the facility classification. The laundry of the staff was managed within the site. Eating, drinking, and smoking was prohibited outside the designated areas.

12. Premises

The following premises were situated in the Main building.

- Offices, ancillary areas
- Warehouses, including primary packaging storage, secondary packaging storage, raw material (actives, excipients) storage, finished material storage, sampling rooms and dispensing rooms.
- Production and packaging areas
- Quality control, utilities, AHUs, water system, filter washing area, document store.

To increase the storage capacity, additional external warehouse has been constructed adjacent to the facility. The warehousing capacities have been increased by this new warehouse and it was not fully operational at the time of the inspection because of on-going qualification and construction work.

HVAC systems
Walked through HVAC area, appeared clean and well maintained. The air-handling units were operated as required by the production program. There was a provision in place that the AHU should be switched on before the starting of the manufacturing activities in the concerned cubicles.

The environment in the production areas was controlled. Every manufacturing cubicle had a separate AHU. Since the last WHO inspection, several new AHUs were installed. The change control, installation, qualification, and monitoring of a new AHU was reviewed and discussed.
The HVAC systems and LAF validation schedule and the SOP summarized the requirement on regular monitoring tests and its frequencies. The details of last testing for particle count, HEPA pressure difference, air change, recovery and microbiology monitoring were checked and found acceptable generally.

Water system
The water system was visited, including source water pre-treatment, purified water generation and distribution system. TOC, PH, conductivity monitoring was online. The company was in change control to expand the distribution loop capacity, this should be followed in next inspection.

Purified water trend analysis: An APQR approved in April 2022 was reviewed. The data was checked and was within specified limits.

Utilities
The diesel electricity power generator served the entire facility in case of electricity breakdown. The procedures were in place in case of power failure.

Pest control
The facility pest control covered insects, spiders, snakes and rodents. The task was managed by the QA and performed regularly by a contract partner according to the SOP.

13. Equipment

Design and construction
Equipment installed in the production block was multi-purpose and each piece of equipment had a unique identification number. The equipment viewed appeared to be of suitable design and construction for the allocated process in general. The primary packaging machine and packaging PV used in tablets production was checked and discussed during the inspection.

Equipment maintenance
The preventive maintenance program covered the production and quality control equipment (General policy and Validation Master Plan). The maintenance policy and schedule for year 2022 was approved and documented. The maintenance protocols and reports of several equipment were reviewed during the inspection.

14. Materials

All the starting materials were purchased from approved suppliers. The active substances, excipients, primary packaging materials and secondary packaging materials were managed upon relevant SOPs. The materials were in the warehouse maintaining ambient (below 25 ^{0}c) and cold (2-8 ^{0}C) temperature and managed by a SAP system. The HVAC of the warehouses supplied filtered air and maintained the required temperature. The temperature was recorded on-line. Printed packaging materials were stored in restricted access. Status control was managed by the Inventory Management.

All the starting materials including active substances, excipients, primary packaging materials and secondary packaging materials should undergo a formal release procedure. The release was recorded in the SAP. Material dispensing was done by trained persons into labelled polybags and containers on FIFO/FEFO.

15. Documentation

The documentation system was basically paper based with scanning of originals and keeping copies electronically according to approved written procedures by QA department. In general, documentation was designed, prepared, reviewed and distributed according to a documented procedure.

A batch numbering system was in place. They were managed according to the SOP for batch numbering system for inward and inhouse produced material (Formulation) and the SOP on flow for generation, approval and issuance of master batch document, batch record and handling of excess material. Batch numbers were generated by the SAP system. Batch production records (BMRs) were retained for each batch processed.

16. Good practices in production

The manufacturing processes were performed and recorded according to instructions in the batch production records. The production of Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate Film-coated Tablet, 50mg/300mg/300mg DLT 50/300/300mg in different production stages was in operation at the time of inspection. The batch manufacturing records of the products under processing were spot checked.

The IPC testing (e.g., leak test, tablet weight) was performed in the IPC laboratory, tablet inspection room and punch and die storage room and usage logs were checked and found acceptable. Several production related SOPs were reviewed e.g., SOP for handling of rejects generated during packing and SOP for reprocessing, reworking and utilisation of recoverable.

The manufacturing equipment for the different production steps was located in separated cubicles following the process line in order to avoid cross contamination and mix-up. The environment was classified and maintained as ISO 8 based on the controlled air supply and the gowning procedures. The environmental conditions were continuously and regularly checked including physical and microbiology testing.

17. Good practices in quality control

The Quality Control department reported to the QA/QC head therefore it was independent of the production. The Physic-chemical laboratory and microbiological laboratory were in place and visited.

The QC department had the following main functions.

- Sampling, receipt, registration of samples together with the issuance of the AR number
- Maintenance of reference materials (compendial and working standards)
- Stability program, including sampling maintenance and testing of stability samples
- Contribution in the investigation of complaints, deviations OOS, OOT results
- Sampling and testing of environmental analysis samples
- Testing of water

Testing of starting materials and finished products

QC testing was conducted as specified in the relevant specifications and according to documented test methods. Samples for testing were kept in a designated area. The tests were recorded on worksheets, data were reviewed by the competent person and finally approved by QC manager.

The test records together with the product specifications and the standard test procedures of Artemether/Lumefantrine Tablet 20mg/120mg were reviewed and discussed. Out of Specification (OOS) / Out of trend (OOT) results, incidents observed during analysis were investigated.
To support the good documentation practices Laboratory Information Management System Software (LIMS) was recently implemented.

Analytical instrument calibration and maintenance

HPLC calibration was checked. The maintenance reports of the last two preventive maintenances were available. The certification, usage and maintenance of HPLC columns was recorded. The records of the column were reviewed and discussed.

The analytical balances were regularly checked according to the detailed SOP (Handling, operation maintenance and calibration of analytical balance). Calibrated standard weights were used for the calibration and verification.

Reserve samples

Reserve samples were kept. The stability samples and retention samples managed by the QC were available.

Reference materials

The incoming reference materials (including compendial standards and working standards) were recorded in a registry. Working standards, were received from the corporate site of preparation and certification. Certificates were available. The inventory, usage logs and the reference working standard CoAs of Artemeter and Lumefantrine were checked. Reference materials were stored in cold chamber (2-8 ^{0}C) or in a room temperature cupboard.

HPLC Data management

The access control for the HPLC system was regulated by SOP for user management policy and adhered. The user groups and their privileges were well-defined and documented.

OOS and OOT management

The following documents were in place and reviewed.

- SOP for OOS and OOT investigation procedure.
- SOP for investigational of aberrations in microbiological test results.
- Trend analysis of OOS Jan-Jun 2022 reviewed and found to be acceptable.

Stability study

Stability study was managed according to SOP for stability study. Stability batches for new product, stability batch for ongoing study and relevant requirement for charging into chamber were well defined. Stability study data of Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate Film-coated Tablet, 50mg/300mg/300mg at condition of 40C 75%, 30C 75%, were checked during the inspection.

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 Quality Chemical Industries Ltd,*** located at ***Plot 1-7, 1st Ring road, Luzira Industrial Park, P.O. Box 34871, Kampala, Uganda*** 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-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2*** https://www.who.int/publications/m/item/trs986-annex2

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*** https://www.who.int/publications/m/item/annex-2-trs-957

3. 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
https://www.who.int/publications/m/item/trs-1025-annex-4

4. 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 1019, Annex 3***
https://www.who.int/publications/m/item/trs1019-annex3

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

6. 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. 957, Annex 1***
https://www.who.int/publications/m/item/trs957-annex1

7. 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://www.who.int/publications/m/item/trs957-annex3

8. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2. ***Short name: WHO TRS No. 1044, Annex 2***
TRS 1044 - 56th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations

9. WHO guidelines on transfer of technology in pharmaceutical manufacturing. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4. ***Short name: WHO TRS No. 1044, Annex 4***
TRS 1044 - 56th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations

10. 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***
https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs961-annex9-modelguidanceforstoragetransport.pdf?sfvrsn=b80e925f_5

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

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

13. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. ***Short name: WHO TRS No. 981, Annex 2***
https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs981-annex2-who-quality-risk-management.pdf

14. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3. ***Short name: WHO TRS No. 981, Annex 3***
https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/prequalification/trs981-annex3-who-variations-prequalified-product.pdf?sfvrsn=809e81b_2

15. 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***
https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs992-annex4.pdf?sfvrsn=2a1980f0_2

16. 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***
https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs992-annex5.pdf?sfvrsn=99aedfbe_2

17. 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. ***Short name: WHO Multisource guidance*** or ***WHO TRS No. 996, Annex 10***
https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs966-annex10.pdf?sfvrsn=5d94f486_2

18. 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

19. 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***
https://extranet.who.int/pqweb/sites/default/files/documents/TRS1010_Annex10.pdf

20. 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***
https://www.who.int/publications-detail/978-92-4-000182-4

21. 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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22. 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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23. Points to consider when including Health-Based Exposure Limits (HBELs) 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 1033, Annex 2***
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24. 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 1033, Annex 3***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

25. 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 1033, Annex 4***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations