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**Prequalification Unit Inspection Services**
**WHO PUBLIC INSPECTION REPORT**
**Finished Product Manufacturer**

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Name of manufacturer | **Fabrica Nacional De Medicamentos SA (Maputo)** |
| Corporate address of manufacturer | 3016 Ave Angola, Maputo, Mozambique |
| **Inspected site** | |
| Name & address of inspected manufacturing site if different from that given above | Parcela 726, Avenida das Industrias Machava, Maputo-Mozambique. |
| Unit / block / workshop number | **General Block:** manufacturing of non-beta-lactam OSD products. |
| **Inspection details** | |
| Dates of inspection | 13 – 17 November 2023 |
| Type of inspection | Initial inspection |
| **Introduction** | |
| Brief description of the manufacturing activities | Production, quality control and release of non-beta-lactam OSD products. |
| General information about the company and site | Fabrica Nacional de Medicamentos SA (FNM) is located at Machava, Maputo, Mozambique. It is a subsidiary of the Mozambique Holdings Limited. This facility included the manufacturing and packaging of tablets, capsules and dry powder suspension/solution in two separate production buildings. One is for the manufacturing of non-beta lactam category oral solid products in the General Block, and the other one is for the manufacturing of beta-lactam OSD products in the Beta lactam Block. |
| History | This was the first WHO GMP onsite inspection. The site was regularly inspected by the NRA: Autoridade Nacional Reguladora De Medicamentos (ANARME), Mozambique. |
| **Brief report of inspection activities undertaken Scope and limitations** | |
| Areas inspected | • Quality management system<br>• Production block<br>• Warehouse<br>• QC laboratories<br>• Water system<br>• Compressed air |
| Restrictions | The inspection was restricted to the manufacturing of the product listed in the inspection scope. |
| Out of scope | Production block/facility that was not used for WHO PQ products were not inspected. |
| WHO products numbers | HA688 Dolutegravir (sodium)/Lamivudine/Tenofovir disoproxil fumarate |

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| covered by the inspection | (DLT) Tablet, Film-coated 50mg/300mg/300mg |

| Abbreviations | Meaning |
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| 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 |

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| 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 (where applicable)** |
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**1. Pharmaceutical quality system**

A documented system for quality assurance was established, with procedures covering key quality elements in place. The Quality Department was divided into QA and QC and were separate from the Production Department. Operations were specified in written form and critical GMP requirements were essentially being met.

***Annual Product Quality Review***

The company had in place a procedure for performing product quality reviews. APQRs are performed annually for the period from January to December. The SOP /QA/040/R1 "Product quality review" as a general description for APQR was in place and included the purpose, scope, responsibility and procedure. It required APQRs to be performed even when no batch was produced during the review period. The APQR for DLT tablets for the period from January to December 2022 "PQR/SFM0058/2022" was reviewed and discussed.

***Quality Risk Management (QRM)***

The SOP "Quality risk management" was reviewed. The QRM process included mapping, risk assessment, risk control, risk communication, and periodic risk review. The risk assessments completed at the time of inspection were recorded. The risk assessment related to cross contamination in General Block performed in June 2023 was checked.

***Management review (MR)***

The SOP "Quality system review" was reviewed. The procedure required MR to be performed regularly with the attendance of the senior management. The report for the MR meeting held in October 2023 was reviewed. The information on key elements of QMS was reviewed and documented.

***Change Control***

The SOP "Change management" was reviewed. Changes were classified as major or minor. The risk assessment was required to be performed depending on the criticality of the change. The CC register for 2023 and several changes were checked.

***Deviations***

The SOP "Deviation Management" was reviewed. The SOP was applicable to deviations related to procedures, processes, environment, equipment, utilities, material, specifications or quality systems, receipt, storage, manufacture and testing of materials, in process products, finished products, drug product containers and closures. Deviations were classified as critical, major, or minor. A deviation observed in the material dispensing cubicle during the inspection was discussed.

***OOS/OOT investigation***

The SOP "Handling of OOS Results" and the SOP "Handling of OOT Results" were reviewed. The OOS registers for 2022 and 2023 were available and checked.

***Root cause analysis***

The SOP "Root cause investigation" was checked. The procedure defined the method to conduct an investigation for any unexplained non-conformance event, including failure of batch, or any of its component, to meet any of its specification. Timeline was specified. If an extension was needed, an approval was required.

***CAPA***

The SOP "Corrective and preventive actions" was spot checked. SOP was applicable to complaints, recalls/returns, deviations and others.

***Product release***

The SOP "Release of finished product" was reviewed. QA was responsible for the final review of all relevant documents including BMR, BPR and batch testing record for the release of finished products according to the SOP. No commercial batches of WHO grade of Dolutegravir/Lamivudine/Tenofovir disoproxil fumarate (DLT) Tablet, Film-coated 50mg/300mg/300mg (HA688) produced from this site had been released yet.

***Electronic data management***

An ERP computerised system was used for material management. No Computerized system was used in production and QC.

The following SOPs/documents were checked:

- SOP "User access management for computerised system"
- SOP "backup and archival of computerised system"
- SOP "Data restoration of computerised systems"
- SOP "Management of data integrity"

**2. Good manufacturing practices for pharmaceutical products**

Good manufacturing practices were generally implemented. Necessary human and physical resources with adequate premises, equipment and utilities were provided for the current operational level of FPP activity. Manufacturing processes were generally adequately defined. The manufacturing processes follow procedures as defined and documented in the BMRs and BPRs. The personnel were appropriately qualified and adequate training was conducted.

**3. Sanitation and hygiene**

Premises and equipment in the FPP production area were generally maintained at an acceptable level of cleanliness at the time of inspection. Personnel at the site were seen to be performing their duties in an organized and diligent manner. Personal hygiene and sanitation appeared generally satisfactory.

**4. Qualification and validation**

***Validation master plan***

The Site Validation Master Plan was reviewed. The VMP included process validation, cleaning validation, considerations for cleaning procedures, analytical methods and sampling techniques, hold time studies, cleaning verification, cleaning monitoring program and handling of new products. VMP also included qualification of building and facilities, temperature mapping, qualification/validation of utilities- heating, ventilation and air conditioning system, water system, compressed air system, analyst qualification, vendor qualification and others.

***Process validation***

The process validation for WHO DLT Tablets 50 mg/300 mg/300mg was reviewed. This was a prospective validation included dispensing, sifting, lubrication and blending, compression, coating and inspection. The batch size was specified. The production equipment list was documented, and the production environment condition was controlled for temperature and relative humidity.

The PV protocol and report for the production and packing validation for Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate Tablets 50 mg/300 mg/300 mg were also reviewed. The content included purpose, scope, type of validation, responsibility, product details, reference documents, validation strategy, and validation report. The ingredients details of the product, with the material codes and the manufacturer were documented. Ingredients were Dolutegravir/Lamivudine/Tenofovir Disoproxil Fumarate (Premix) produced and supplied by a Mylan manufacturing site located in India. No Deviations were recorded during the execution of the PV.

***Continuous Process Verification (CPV)***

The SOP "Process Validation" was reviewed. The CPV was required to be performed for each commercialized product to ensure that the manufacturing process remains in a state of control. A template was designed which detailed that there will be a regular review.

***Cleaning validation***

The SOP "Cleaning Validation" was reviewed. The SOP outlined the procedure for performing the validation and verification of cleaning procedures at FNM, including the responsibilities for performing and approving the cleaning validation/verification studies, acceptance criteria and when revalidation was required. The SOP purpose was to demonstrate that no cross contamination occurred and that the current cleaning procedure was validated and can consistently clean the equipment. A product list for the shared equipment was available. Determination of the worst-case product and establishment of product matrix was documented.

***HVAC system qualification/validation***

The HVAC system providing filtered air to the Grade D cleanrooms of General Block was spot checked. The configuration and qualification of AHUs was documented. The terminal HEPA integrity result was showed within specifications. The potential risk of air exhaustion from the nearby Beta lactam Block was also discussed.

## 5. Complaints

The SOP "Management of Market Complaints" was reviewed. The procedure mandated that complaints received had to be logged and handled for investigation. The log for complaints included receipt date, complainant, product name, batch number, brief description of complaint, market, complaint substantiated or non-substantiated, classification, date of response, and closure date. Complaints log for 2023 was reviewed and discussed.

**6. Product recalls**

The SOP "Product recall" was checked. Recall was classified as Class I, Class II or Class III upon the level of the defect. The product with WHO PQ programme has not been yet supplied to markets. No batch has been recalled.

***Return***

The SOP "Handling of returned and salvaged goods" was available, and spot checked.

**7. Contract production, analysis and other activities**

Contract production, analysis and any other activity covered by GMP were defined, agreed and controlled. Mylan Laboratories is the applicant of HA688 DLT Film-coated Tablet, 50mg/300mg/300mg, FNM was additional manufacturing site for the tablets produced starting from DLT Premix. The technical agreement (TA) between Mylan Laboratories Limited (Contract Giver) and Mozambique Holding Limited (Contract acceptor) was presented and checked.

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

***Self- Inspection***

A self-inspection plan and SOP was in place. This was spot checked in the management review and not reviewed in detail.

***Supplier qualification and approval***

The SOP "Vendor Audit" was reviewed. The procedure defined that if any new supplier to be added to FNM e.g., new products, new RM, new packing materials, new sources, the addition had to follow a change control process. The "Quality risk management for vendor management" was checked.

**9. Personnel**

An organization chart was available. Key personnel responsibilities were required to be defined in job descriptions. Job descriptions for QA head, QC head and Production head were checked and found generally acceptable. FNM had an adequate number of personnel with the necessary qualifications and practical experience.

**10. Training**

Training was not checked in detail during this inspection because of time constraints. One training file of a staff working in IPC lab was checked and discussed.

**11. Personal hygiene**

Personnel hygiene requirements for entry to Grade D cleanrooms were checked. The pictorial drawings were displayed in change rooms. The procedure implementation was checked and discussed.

**12. Premises**

The site has four independent blocks, named (1) General, (2) Beta lactam, (3) Admin and (4) Central Stores.

***Warehouses***

Storage areas in Central Stores for warehousing of starting materials, packaging and finished product were of sufficient capacity. Temperature and humidity were monitored manually. Receiving and dispatch bays were separated and were protected from weather conditions.

The General Block and Beta lactam Block had separate storage areas for handling approved and rejected materials according to the company. The Central store and storage area in General Block were briefly visited.

Fully finished packs in shippers were stored in the FG warehouse. Temperature and relative humidity monitoring were performed and recorded. The data logger was placed in the hot spot identified via temperature mapping.

***Production***

The General Block was multi-product and not dedicated. Manufacturing areas were of an acceptable standard and suitable for the activities conducted therein. Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated cleaning. The classified areas were monitored manually for temperature, relative humidity and pressure differentials for environmental control.

***QC Labs***

QC laboratories were separated from production areas.

***Purified water***

Water system was briefly visited. The P & ID of PW system was documented. PW was produced from bore well water by double ROs followed by EDI. PW in QC was generated by a water purification system.
The SOP "Operation and maintenance of purified water generation system" and the SOP "sampling and testing of water for microbiological quality" were checked. The alert and action limit of TAMC for PW were specified. PW annual review report for the period from January to December 2022 for General Block was available for review.

***Compressed air***

The generation system for the compressed air supplying the General Block was briefly visited.

***Pest control***

The area had an insectacutor present on the inside of the Central stores and was checked.

## 13. Equipment

Equipment installed in General Block was multi-purpose and each piece of equipment had a unique identification number. The equipment appeared to be of suitable design and construction for the allocated processes.

***Equipment maintenance***

The equipment viewed during the inspection appeared to have been suitably maintained and in good condition. Equipment status labels were available.

The SOP "Procedure for preventive maintenance" was reviewed. The preventive maintenance schedule was required to be prepared for in advance. The maintenance schedule for 2023 was presented. The maintenance record of a compression machine was verified.

***Equipment cleaning***

Equipment cleaning was performed following written procedures. The following SOPs were checked.

- SOP "Operation and Cleaning Procedure for Octagonal Blender".
- SOP "Operation of cleaning of high-pressure cleaner".

- SOP "Operation and Cleaning of Compression Machine C 300 49 D".

***Equipment calibration and qualification program***

The SOP "Calibration Policy" was reviewed. The purpose was to provide for the calibration of all measuring and testing/controlling instruments and devices as well as weighing scales and standard weights. Instruments and measuring devices were divided into critical and non-critical. A calibration plan was compiled.

## 14. Materials Management

The starting material and finished goods were managed by ERP and manual hybrid system. They were quarantined after receipt until released for use or distribution. Status of raw material was indicated, with respect to material under quarantine, approved, etc. The approved vendor list was presented.

The starting materials and packaging materials were checked, quarantined, sampled and released/rejected following in house procedures. The raw material sampling log was spot checked. The reject store was not located in the warehouse in which the inspection took place and the company confirmed the reject store was in another area located in the General Block. The area was visited during the inspection.

Material's sampling, code management, status, location and movement of starting materials and finished products of DLT tablets in the ERP system were checked and discussed.

## 15. Documentation

The SOP "Document management" was reviewed. Documents were managed using a manual system under the responsibility of the QA department. Documentation was designed, prepared, reviewed and distributed according to an approved procedure. Retention period for different documents were specified. Approved specifications for starting, packaging materials and finished products were available.

***Batch numbering system and BMR management***

The SOP "Batch numbering" and SOP "Handling MFR/BMR/BPR" were reviewed. The authorized master formula records were available for commercialised products. Batch manufacturing records (BMRs) were retained. BMRs for DLT tablet, 50 mg/300 mg/300 mg were checked.

## 16. Good practices in production

The manufacturing processes were performed and recorded according to instructions in the batch production records. DLT tablet's manufacturing steps including material dispensing, sifting, blending, compression, coating, IPC along with primary, and secondary packaging in General Block were inspected.

DLT premix blending activity was not in operation at the time of inspection. Manufacturing records of another product under granulation was spot checked and found acceptable. However, the DLT tablets were under processing in Compression, Coating and Packing operation. In-process controls were conducted at IPC laboratory inside of the General production block.

The SOP "Reprocessing and reworking" was reviewed and discussed.

## 17. Good practices in quality control

The QC function was independent of other departments. QC laboratory was separated from production areas. It was housed in the admin building including microbiological laboratory. The microbiology laboratory was segregated from the chemistry laboratory.

***Sample receiving and distribution***

An access-controlled area for sample receipt was available. Sample register and the information for receiving and distribution were checked. The traceability of raw data was available in the sampling records. The procedures reviewed and discussed during the inspection were generally of an acceptable standard.

***Testing of starting material and finished products***

The procedure for testing and release of raw material and procedure for bulk and finished product release procedure were available. The procedures were checked, e.g.,

- SOP "Sampling, testing, release/reject of raw materials"
- SOP "Reporting of analytical results"
- SOP "Preparation and handling of working standard"

***Retention samples***

Retention samples were kept in a secured and temperature-controlled room. The retention sample register and samples of each batch were kept. Annual check for the sample was performed according to the company procedure.

***Stability study***

Stability study room was briefly visited. "Stability studies" SOP was in place. The stability study protocol for WHO grade of DLT tablets and the stability data for process validation batches were checked and appeared acceptable.

***Instrumentation***

The company has adequate numbers of instrument and equipment for QC laboratories. The chromatographic analysis instrument including four HPLC and GC were standalone. The records and logs were maintained. Status labels were attached to equipment and found acceptable.

***Microbiology Laboratory***

Microbiology Laboratory was visited. This area was accessed via the Entry to QC. The following aspects were checked, but not limited to:

- Entry and exit,
- The SOP "Personal entry and exit procedure to quality control" where the gowning procedure was verified.

Media storage and preparation

The SOP "Receipt, Preparation and Storage of Culture Media" was reviewed. The purpose of the mentioned procedure was to provide guidance for receipt, preparation, and storage of media. Purified water was used to prepare the media.

Growth Promotion

The SOP "Growth promotion and, inhibitory properties of the media" was reviewed. The purpose of the mentioned procedure was to provide guidance for the promotion, inhibitory, and indicative tests for the received media.

Media hold times

The SOP "Receipt, preparation and Storage of Culture Media" was reviewed. The holding time for the prepared solid media was specified.

| Part 3 | Conclusion – Inspection outcome |
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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, ***Fabrica Nacional De Medicamentos SA*** located at ***Parcela 726, Avenida das industrias Machava Maputo, Mozambique*** 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***
   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 guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
   ***Short name: WHO TRS 1010, Annex 9***
   https://www.who.int/publications/m/item/trs1010-annex9

4. 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***
   https://www.who.int/publications/m/item/annex-3-trs-1033

5. 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/annex-4-trs-929

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. 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/publications/m/item/Annex-8-trs-1010

9. 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**
   https://www.who.int/publications/m/item/trs1019-annex2

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    ***Short name: WHO TRS No. 1044, Annex 4***
    https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1044-annex4-technology-transfer-in-pharmaceutical-manufacturing.pdf

11. WHO good manufacturing practices for sterile pharmaceutical products. Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    ***Short name: WHO TRS No. 1044, Annex 2***
    https://www.who.int/publications/m/item/trs1044-annex2

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***
https://www.who.int/publications/m/item/trs943-annex3

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.
***Short name: WHO TRS No. 961, Annex 2***
https://www.who.int/publications/m/item/trs961-annex2

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.
***Short name: WHO TRS No. 981, Annex 2***
https://www.who.int/publications/m/item/trs981-annex2

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.
***Short name: WHO TRS No. 981, Annex 3***
https://www.who.int/publications/m/item/annex-3-trs-981

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.
***Short name: WHO TRS No. 961, Annex 14***
https://www.who.int/publications/m/item/tr961-annex14

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***
https://www.who.int/publications/m/item/trs1019-annex3

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***
https://www.who.int/publications/m/item/trs992-annex4

19. 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://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

20. 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://www.who.int/publications/m/item/trs992-annex5

21. 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/trs-992-annex-6

22. 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***
https://www.who.int/publications/m/item/annex-4-trs-1033

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
***Short name: WHO TRS No. 996, Annex 10***
https://www.who.int/publications/m/item/trs966-annex10

24. 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://www.who.int/publications/m/item/trs1010-annex10

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**
https://www.who.int/publications/m/item/annex-2-trs-1033

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**
https://www.who.int/publications/m/item/trs-1025-annex-6

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***
https://www.who.int/publications/m/item/trs-1025-annex-3-water-for-injection

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***
https://www.who.int/publications/m/item/trs1025-annex4