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**Prequalification Team Inspection services**
**WHO PUBLIC INSPECTION REPORT**
**WHOPIR**
**Active Pharmaceutical Ingredient Manufacturer**

| **Part 1** | **General information** |
|---|---|
| **Manufacturers Details** | |
| **Company information** | |
| Name of manufacturer | Aragen Life Science Limited |
| Corporate address of manufacturer | Plot No. 28A, IDA,<br>Nacharam Village, Uppal Mandal,<br>Medchal-Malkajgiri District,<br>Hyderabad City-500076, Telangana State, INDIA |
| **Inspected site** | |
| Address of the inspected manufacturing site if different from that given above | Same as above |
| Production Block/ Unit | Block A, Unit 1 |
| **Inspection details** | |
| Dates of inspection | 12 -16 June 2023 |
| Type of inspection | Initial inspection (On-Site) |
| **Introduction** | |
| Summary of the manufacturing activities | Production and quality control of APIs and API Intermediates |
| General information about the company and site | The site was set up in 2005 and named as Aragen in December 2020. The site offers process development and optimization services across multiple therapeutics and chemistry discipline, as well as commercialization of APIs and intermediate. The facility is located about 35 km away from Hyderabad Airport.<br>No beta-lactam antibiotics, hormones or cytostatic APIs were manufactured on-site according to the company's information. |
| History | This was the first onsite WHO inspection of the site. |
| Brief report of inspection activities | |
| **Scope and limitations** | |
| Areas inspected | • Quality management system<br>• Production Block: A<br>• Warehouses for starting materials and finished API products<br>• Physical and Chemical laboratory<br>• Microbiology laboratory<br>• Water system |

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| | • Nitrogen system |
| Restrictions | The scope of the inspection was restricted to the following API in the WHO PQ program. |
| Out of scope | The production and quality of micronized Moxifloxacin hydrochloride was not included in the dossier and was not inspected. |
| WHO product numbers covered by the inspection | APIMF205 Moxifloxacin hydrochloride |

| **Abbreviations** | **Meaning** |
|---|---|
| AHU | air handling unit |
| ALCOA | attributable, legible, contemporaneous, original and accurate |
| API | active pharmaceutical ingredient |
| APQR | annual product quality review |
| BDL | below detection limit |
| BMR | batch manufacturing record |
| BPR | batch packaging record |
| CAPA | corrective actions and preventive actions |
| CC | change control |
| CFU | colony-forming unit |
| CoA | certificate of analysis |
| CpK | process capability index |
| cGMP | Current Good Manufacturing Practices |
| DQ | design qualification |
| DHT/CHT | Dirty holding time/clean holding time |
| EM | environmental monitoring |
| FAT | factory acceptance test |
| FBD | fluid bed dryer |
| FMEA | failure modes and effects analysis |
| FPP | finished pharmaceutical product |
| FTA | fault tree analysis |
| FTIR | Fourier transform infrared spectrometer |
| GC | gas chromatograph |
| GMP | good manufacturing practice |
| HACCP | hazard analysis and critical control points |
| HPLC | high-performance liquid chromatograph |
| HVAC | heating, ventilation and air conditioning |
| IR | infrared spectrophotometer |
| IQ | installation qualification |
| KF | Karl Fisher |
| LAF | laminar air flow |
| LIMS | laboratory information management system |
| LoD | limit of detection |
| LOD | loss on drying |
| MB | Microbiology |
| MBL | microbiology laboratory |
| MF | master formulae |
| MR | management review |

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|---|---|
| NMR | nuclear magnetic resonance spectroscopy |
| NRA | national regulatory agency |
| OQ | operational qualification |
| OOT | Out of Trend |
| PHA | process hazard analysis |
| PM | preventive maintenance |
| PpK | process performance index |
| PQ | performance qualification |
| PQR | product quality review |
| PQS | pharmaceutical quality system |
| PV | Process Validation |
| PW | Purified Water |
| RH | Relative Humidity |
| 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 |
| SAP | System applications and product in data processing |
| SOP | standard operating procedure |
| TAMC | total aerobic microbial count |
| TFC | total fungi count |
| TLC | thin layer chromatography |
| TRS | Technical Report Series |
| URS | user requirements specifications |
| UV | ultraviolet-visible spectrophotometer |
| XRD | X-Ray diffraction |

| **Part 2** | **Summary of the findings and comments** |
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## 1. Quality management

A formal 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 met. Product and processes were monitored, and these results were considered during batch release. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard.

**Product quality review (PQR)**

The SOP for product quality reviews and the following APQR for Moxifloxacin hydrochloride were reviewed.

***APQR for Moxifloxacin hydrochloride***

Approved on 27/03/2023.

Review period: January to December 2022.
The API product code for WHO and for domestic market was specified. There were several quality specifications approved for the API. The batches produced during the review period for the intermediate, bulk and finished API of Moxifloxacin hydrochloride were reviewed, including change control, deviation, OOS, OOT and CAPAs.
No complaint, recall, return, reprocessing and reworking were reported. The company declared that the recovered materials and solvents were not used to produce WHO grade Moxifloxacin hydrochloride.

***Quality Risk Management***
Quality risk management and risk assessment were managed and performed according to an approved SOP. Several risk assessment reports were checked, and they were prepared using the FMEA tool.

***Management review (MR)***
Management review was a corporate responsibility that followed a written procedure, which required MR to be performed every six months and chaired by Chief Executive Officer with the attendance of senior management. The meeting report for the MR held in January 2023 was reviewed. The implemented and unclosed actions in QMS were documented.

***Deviation***
The SOP for deviation management was checked. Two deviations with respect to the production yield of Moxifloxacin API were checked. A change control for the range of yield was initiated after the investigation. The investigation was performed in compliance with SOP.

***CAPAs***
CAPAs were managed according to an approved SOP. The CAPA report checked showed the CAPA process was performed in compliance with the SOP.

***Product release***
The SOP for product release for all saleable intermediates and APIs was reviewed. The QA staff performed the final product release. The release for two batches of Moxifloxacin hydrochloride was reviewed and discussed.

***Internal audits***
The SOP for internal quality audits was reviewed. The SOP contained a "check list." The audit schedule was prepared once a year and the audits were performed regularly in each area. The CAPAs were required to be verified by auditors in the next inspection. The qualified auditors were documented in the "List of Quality Auditors."

## 2. Personnel
An organization chart was available. The Quality Department was divided into QA and QC teams, separate from the production department. There was an adequate number of personnel suitably qualified by education and training to perform and supervise the manufacturing of APIs. The company had 351 full-time employees for this site at the time of this inspection.

***Personnel qualifications***

The personnel met during the inspection appeared to be knowledgeable about GMP. Key personnel responsibilities were required to be defined in job descriptions. The job descriptions and responsibilities of site manager for QA, QC and Production were available for review.

***Personnel hygiene***

Personnel were required to wear protective clothing suitable for the type and stage of manufacturing. Sanitation and change room facilities were provided. The gowning procedure in the microbiological laboratory to access Grade C area was checked and discussed.

***Training***

The SOP for training was checked. The cGMP training was required to be performed for all employees yearly and the attendance was mandatory for each session. The annual plan for cGMP training was prepared. The training records of QA and QC staff were spot checked and found to be acceptable.

## 3. Buildings and facilities

***Production***

There were three production blocks employed in API production at the site. The production of Moxifloxacin hydrochloride was employed in Block A. The chemical synthesis area, intermediate drying areas and a clean room in Block A were visited. The final Moxifloxacin hydrochloride API crystallization, centrifuging, drying and packaging took place in the classified clean area.

***QC Laboratory***

The QC Laboratories including the Physical/Chemical laboratory and Microbiological laboratory were located in a separate building. They were briefly visited.

***Water system***

The PW system was briefly visited. The source water from the Hyderabad metropolitan water supply was used to produce process water and PW. The piping and instrumentation diagram (P & ID) for water system was reviewed. The on-line operational and control parameters, such as conductivity and flow rate were within the limits. The PW testing and monitoring results spot checked appeared acceptable.

***Nitrogen***

Nitrogen system was briefly visited. The P & ID of the nitrogen system and sampling points were documented. The testing for nitrogen was performed regularly by an external contract laboratory located in Hyderabad, India. The SOP for nitrogen testing and the nitrogen testing results checked showed within the acceptance limits.

***AHUs***

The Air handling units were briefly visited. The filtered air was supplied to the clean rooms in production blocks.

## 4. Process equipment

***Design and construction***

The equipment in Block A used in the manufacture of the API were not dedicated. Tray dryers were used for drying of Moxifloxacin hydrochloride intermediate and finished API. The dust deduction/extraction equipment was installed in the final milling and sifting rooms.

***Equipment maintenance and cleaning***

The SOP for equipment and QC instrument maintenance and the SOP for cleaning of centrifuge was checked. The cleaning process including the volume of solvents, drying and sampling was described in detail in the SOP.

***Computerized systems***

The computerized systems were not used for production control. The computerised systems were used in QMS, document management, material management and quality control.

***Calibration***

The SOP for equipment calibration was checked. The equipment calibration was required to be performed periodically. The annual calibration plan approved in December 2022 was presented for review. The calibration of a stability chamber was checked, which showed the SOP for operation and performance verification of the stability chamber was followed.

***Requalification of QC equipment***

The requalification of a stability chamber was checked. The frequency of requalification was specified. All results checked fulfilled the acceptance criteria (temp. 30±2ºC and humidity 75±5%).

## 5. Documentation and records

***Documentation system***

The SOP for documentation requirements and the SOP for initiation, review, approval, control, distribution, revision and retrieval of documents were reviewed. Activities were described in the SOPs and other appropriate documents such as batch manufacturing records (BMRs). These were all approved, and version controlled. All records and other documentation requested during the inspection were readily available.

***Specifications***

Specifications for starting materials, packaging materials and finished products were appropriately approved and dated. The finished product specifications and method of analysis of Moxifloxacin hydrochloride (WHO grade) were checked. There were several other valid specifications for Moxifloxacin Hydrochloride. The specifications differed in terms of impurities and microbiological tests.

***Batch numbering system***

The SOP for batch numbering system was reviewed. The batch numbers were generated manually for a production batch. A commercial batch number was then assigned for the packaging operation batch according to the procedure.

***Batch production records***

The SOP for managing the BMR insurance and the logbook of BMR insurance were checked. An approved Master BMRs for Moxifloxacin hydrochloride were documented. The BMRs for a Moxifloxacin API batch and the associated records for the intermediates used in this batch were reviewed and discussed.

***Laboratory control records***

The monitoring records of temperature and humidity in a stability chamber (25ºC/RH60%) were checked. All results reviewed fulfilled the acceptance criteria.

## 6. Materials management

***General controls***

The company had SAP systems in place to manage the stating material and packaging material. The system was managed according to the SOP for handling of warehouse management system. The procedures for the receipt, quarantine, storage, handling, sampling, testing and approval or rejection of materials were checked and found generally acceptable.

***Receipt and quarantine***

The SOP for raw and packing material receipt, storage, handling was checked. The documents such as the gate pass, CoA etc. should be verified by the warehouse personnel during receipt of the materials

***Sampling and testing of incoming production materials***

The QC was responsible for sampling and testing of starting materials according to an approved SOP. The sampling was performed in a dedicated sampling room. The tools used for material sampling were stored in a special cabinet in the warehouse.

***Storage***

Starting materials and packaging materials were stored in the separate storage rooms in the raw material warehouse which was in ambient condition without temperature and humidity control but monitoring of the temperature was performed for one hot spot in each room. A washing room and a small cold storage room were located in the warehouse.

The finished product warehouse included the storage rooms for released finished products, for the finished products ready to dispatch and for the rejected, recalled, and returned finished products. All the areas were designated and marked. The temperature in the warehouse was controlled at 25±2ºC. The hot spots in the warehouse were defined. Records indicated that the specified conditions had been maintained.

***Vendor approval and audit***

The SOP for vendor qualification was checked. The procedure covered the vendors for all raw starting materials and packaging materials. The approved list of vendors was verified. The requalification of vendors was performed periodically. The qualifications of selected vendors supplying key starting materials for Moxifloxacin production were verified. These vendors were included on the "Approved Vendor List.

## 7. Production and in-process controls

The Production of Moxifloxacin hydrochloride took place in Block A which was not in operation at the time of inspection. Some other APIs were in operation during the visit. The production and in-process controls were briefly inspected and appeared acceptable generally. The control in the intermediate drying and storage areas, as well as equipment cleaning room were checked and discussed.

***Blending batches of intermediates or APIs***

The SOP for material blending operation was checked. The blending was applied for Moxifloxacin hydrochloride API batches. The blending validation for Moxifloxacin hydrochloride API was discussed.

***Contamination control***

The purification, crystallization and drying for Moxifloxacin hydrochloride was performed with non-dedicated equipment in the non-dedicated clean area of Block A in which the temperature and pressure differential control were in place.

8. **Packaging and identification labelling of APIs and intermediates**

Packaging materials and labels were subjected to quality control before release. Packaging and labelling were not in operation at the time of inspection. Line clearance in the packaging area was spot checked and discussed. The packaging and labelling operations in the batch packaging record reviewed was generally acceptable.

9. **Storage and distribution**

***Warehousing procedures***

Finished APIs were stored in a designated warehouse and held until it is released in the SAP system. The Moxifloxacin hydrochloride API batch release, batch reconciliation and storage location were checked and discussed.

***Temperature mapping***

The temperature mapping was performed according to an approved SOP for the areas where temperature control was required. Two mappings of temperature in the finished product warehouse were checked. The temperature distribution study report for finish goods storage room showed the data met the acceptance criteria for temperature.

***Distribution procedures***

APIs and intermediates were released for distribution by QA following release requirements described in the release procedure.

**10. Laboratory controls**

The physical/chemical laboratory and microbiology laboratory were visited. Procedures were in place describing sampling, testing, approval or rejection of materials as well as recording and storage of laboratory data. Specifications, sampling plans and test procedures were available. The procedures that were reviewed and discussed during the inspection were generally of an acceptable standard.

***Sample receiving and distribution***

The sampling of the finished API took place in the clean room in the production area. Sample receiving procedure and corresponding register were available for inspection.

***Testing of intermediates and APIs***

The QC testing of intermediates and APIs was performed according to the relevant specifications and standard test procedures. The assay test of Moxifloxacin hydrochloride was spot checked. The test was operating in the HPLCs networked with Empower software. The data integrity controls were in place.

The testing of Moxifloxacin hydrochloride for polymorphism by XRD, elemental impurities and Nitrosamine impurities was performed under the contract with "Aragen Life Sciences Limited, Analytical Solutions" located at Survey Nos. 125 (part) & 126, IDA Mallapur, Hyderabad – 500 076,

INDIA a member of the Aragen group. The laboratory was briefly visited. Some testing data for un-micronized batch of Moxifloxacin hydrochloride API was spot checked and discussed.

***Reserve/retention samples***

According to the SOP for reserve sample maintenance, the retention samples comprised key starting materials, saleable intermediates, commercial APIs, and customer-suggested materials. The retention sample room was located in the QC Laboratory with access control. The room temperature was controlled. For finished API products, sufficient quantity was retained to conduct at least two full analyses for every batch. The retained samples were kept in the same packaging materials as the marketed products.

***Handling of out of specification (OOS) and OOT results***

The OOS results including chemical and microbiological tests were managed according to an approved SOP. An OOS for Moxifloxacin Hydrochloride API testing was checked. A laboratory investigation was carried out in compliance with the SOP, and the testing result was confirmed.

The SOP for handling OOT results was checked. There were no OOT reported for Moxifloxacin API reported. OOT testing results for other APIs were checked and showed the investigation was performed in accordance with the SOP.

***Stability study***

The SOP for stability study was checked. The stability study should be carried out in the following situations: initial validation batches, ongoing stability study, major process changes and other specified situations. The temperature and RH conditions for the stability study were specified in the SOP.

Stability samples were stored in a dedicated room in the QC laboratory, in containers that simulated the market containers. The tests and acceptance criteria for Moxifloxacin's stability study were listed in the approved stability study protocol. The Moxifloxacin Hydrochloride PV batches underwent stability studies. The following documents for Moxifloxacin hydrochloride were checked:

- Stability study protocol
- Accelerated stability study data
- Long term stability data
- The ongoing stability study batches for Moxifloxacin Hydrochloride:

The stability tests were performed according to the schedule. All results fulfilled the acceptance criteria.

***Microbiology laboratory***

The microbiology laboratory was briefly visited. The microbiological test for purified water was performed in this laboratory.

The microbiological tests for finished API products and tests of environmental monitoring of clean rooms in production area were performed by contract laboratories.

## 11. Validation

Validation and qualification were described in the Validation Master Plan.

***Process validation***

The SOP for process validation was checked. The process validation was required to be performed either prospectively or concurrently. The process validation protocols and associated validation reports for Moxifloxacin hydrochloride with PV batches were reviewed and found to be acceptable. The validation of blending operation and wet Moxifloxacin hydrochloride API holding time were checked and discussed.

***Qualification***

The SOP for instrument and equipment qualification was reviewed. Qualification of key equipment was a prerequisite for process validation. A change control request for the replacement of a reactor in block A for purification/crystallization of Moxifloxacin hydrochloride and the reactor's qualification report were checked and discussed.

***Computerized system validation***

The computerized system validation was not checked in detail in this inspection due to time constraints.

***Cleaning validation:***

The SOP for cleaning validation was reviewed. The cleaning validation for production line for Moxifloxacin was completed in 2023. The active substances manufactured in this production line were documented. The acceptance criteria were calculated for all the products in this production line. The worst-case acceptance criteria were calculated for the shared equipment.

The cleaning validations for the changeover from other APIs to Moxifloxacin Hydrochloride were performed. The relevant protocols and reports were presented for review. The validation of equipment dirty holding time and clean holding time were also checked and discussed.

## 12. Change control

The SOP for handling change controls was reviewed. The changes were classified as critical, major or minor.

A change control with respect of the yield of Moxifloxacin Hydrochloride API was checked. The change control process was processed and evaluated according to the SOP. The change control was closed.

## 13. Rejection and re-use of materials

***Reprocessing and Reworking***

The SOP for reprocessing and reworking was checked and discussed.

***Recovery of materials and solvents***

Solvents and mother liquors were recovered in the various stages of the production of APIs. The procedure for solvent recovery and reuse was reviewed. The company confirmed no external plant was used for solvent recovery, and the solvent was recovered on the site.

The company declared no recovered solvents/mother liquor were used in WHO grade Moxifloxacin hydrochloride production.

***Returns***

The SOP for handling returned goods was checked and found to be acceptable. The company stated no returned batch for Moxifloxacin hydrochloride API since 2019.

**14. Complaints and recalls**

The SOP for product complaints was checked. The complaints were classified as critical, major, or minor. The QA department was responsible for handling the complaint within specified timelines. The complaints from 2020 to 2023 were checked and no complaints were reported.

The SOP for product recall was checked. The scope and classification of recalls were defined. The mock recall was performed once every two years. The report of the last mock recall held in 2023 was checked and found to be acceptable.

**15. Contract manufacturers (including laboratories)**

***Contract manufacturer***

The SOP for handling of contact manufacturing activities was checked. The detailed requirement for qualification of contract manufacturers was described. The manufacturers and suppliers of key starting materials and intermediate used for WHO grade of Moxifloxacin hydrochloride API production were spot checked for the qualification and audit performed by the company and found to be generally acceptable.

***Contract laboratory***

Contract laboratories were used for testing for API's polymorphism, microbiological limit, elemental impurities, Nitrosamine impurities, nitrogen and compressed air tests. The procedures for managing contract testing service providers, audit report and testing data were spot checked and discussed.

| 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, ***Aragen Life Science Limited*** located at ***Plot No. 28A, IDA, Nacharam*** Village, Uppal Mandal, Medchal-Malkajgiri District, Hyderabad City-500076, Telangana State, 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***
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

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