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**Prequalification Unit Inspection Services**
**WHO PUBLIC INSPECTION REPORT**
**(WHOPIR)**
**Active Pharmaceutical Ingredient Manufacturer**

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Name of manufacturer | Zhejiang Langhua Pharmaceutical Co., Ltd. |
| Corporate address of manufacturer | No.7, Donghai 3rd Avenue,<br>Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone,<br>Linhai,<br>Zhejiang, R.P. China. |
| **Inspected site** | |
| Name & Address of inspected manufacturing site if different from that given above | Zhejiang Langhua Pharmaceutical Co., Ltd.<br>Address: No.7, Donghai 3rd Avenue,<br>Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone, Linhai,<br>Zhejiang. China. |
| Synthetic Unit /Block/ Workshop | Block 110, Block 161 and Block 034 |
| **Inspection details** | |
| Dates of inspection | 16-19 April 2024 |
| Type of inspection | Routine re-inspection |
| **Introduction** | |
| Brief description of the manufacturing activities | Manufacturing and quality control of API and intermediates for human and veterinary use. |
| General information about the company and site | The site was built in 2005 and named Zhejiang Xinhua Pharmaceutical Co., and renamed as Zhejiang Langhua Pharmaceutical Co., Ltd in 2013. The company is an API manufacturer focusing on APIs, pharmaceutical intermediates, and CDMO projects. APIs and intermediates manufactured on-site included therapeutic classes of Quinolone, Cardiovascular, Anti-depressive and Anti-HIV etc. No highly toxic penicillin/cephalosporins or biological origin materials were manufactured on-site. |
| History | This was the fourth on-site WHO PQT inspection with an additional Desk Assessment conducted in 2019. The site was regularly inspected by Zhejiang Medical Products Administration. |
| WHO products covered by the inspection | WHOAPI-203 APIMF203 Levofloxacin hemihydrate<br>APIMF 275 Levofloxacin hemihydrate (Intermediate) |
| **Brief report of inspection activities undertaken – Scope and limitations** | |
| Areas inspected | • Quality management system<br>• Production blocks<br>• Warehouses<br>• Tank farm<br>• QC laboratories<br>• HVAC system<br>• Purified water system |

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| Restrictions | The scope of the inspection was restricted to the API and intermediate in the WHO PQ programme. |
| Out of scope | APIs which are not under the scope of prequalification. |
| **Abbreviations** | **Meaning** |
| AHU | Air handling unit |
| ALCOA | Attributable, legible, contemporaneous, original and accurate |
| API | Active pharmaceutical ingredient |
| APR | Annual product review |
| BER | Batch Analysis Record |
| BMR | Batch manufacturing record |
| BPR | Batch production record |
| CC | Change control |
| 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 |
| 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 |
| KF | Karl Fisher |
| LAF | Laminar air flow |
| LIMS | Laboratory information management system |
| MB | Microbiology |
| MBL | Microbiology laboratory |
| MR | Management review |
| NC | Nonconformity |
| 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 |
| QP | Qualified person |
| QMS | Quality management system |
| QRM | Quality risk management |

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|---|---|
| RA | Risk assessment |
| RCA | Root cause analysis |
| RO | Reverse osmosis |
| 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 management**

A system for managing quality was established based on guidelines for Good Manufacturing Practices for APIs, Quality Risk Management, and Pharmaceutical Quality Systems. A system that involved the participation of management and appropriate manufacturing personnel was in place. Quality-related activities were defined and documented. The Quality department consisted of Quality Assurance and Quality Control and was independent from the Production department. Responsibilities of the Quality Unit and Production Unit were addressed in SMP and found acceptable. QA, together with persons authorized to release intermediates and APIs, were specified.

**2. Personnel**

The site employed 510 employees at the time of the inspection. The company had an organization chart that showed there was separation between the responsibilities and reporting of the Quality Unit and Production units. Responsibilities were defined and documented in the job descriptions for all staff. The job descriptions of the Vice General Manager (Quality Head and Qualified Person), QA Managers, QC Manager and Production Director were checked.

***Training***

An adequate number of qualified trained and experienced personnel was available. Training was addressed in the "SMP of Training". The SOP was applicable to new employees and current employees. Ongoing GMP / quality training was provided. Written training records were kept for all employees. Training records were verified and found compliant.

***Hygiene***

Personnel were trained to practice good sanitation and health habits. Details were described in the "SMP of personnel hygiene". Direct contact with intermediates or APIs was avoided. Personnel with an infectious disease or who have open lesions on the exposed surface of the body were not engaged in activities that could result in compromising the quality of APIs. Staff undergo a medical examination before joining the company, with an annual medical examination performed for all employees. Employees were required to change uniforms daily, with handwashing facilities available in production areas. Measures were taken to prevent unauthorized people from entering Production and QC areas.

**3. Buildings and facilities**

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities were designed to minimize potential contamination. The buildings were divided into the Chemical production area and the clean area. The differential pressure between adjacent rooms, which have different clean levels, was defined.

Buildings and facilities had adequate space for the orderly placement of equipment and materials. Permanently installed pipework was appropriately identified. Adequate lighting was provided to facilitate cleaning, maintenance, and proper operations.

QC Laboratory areas and operations were separated from production areas. A separate warehouse for starting material and a separate warehouse for finished products were available. All areas were access-controlled.

***Purified Water (PW) system***

Water used in the manufacture of APIs was suitable for its intended use. Two kinds of process water were used, i.e., City water (potable water) and purified water, which was produced by Reverse Osmosis (RO) and complied with the CP/EP/USP monographs.

Three phases of validation of the PW system were performed. PQ of the water system was completed. A purified water (PW) sanitizing and monitoring program was in place. The 2023 Annual PW quality review for a workshop was verified.

***HVAC***

AHUs were providing air to the workshop clean rooms. The "SMP of HVAC system management" was checked. The "SMP of clean room monitoring" specified the monitoring items and frequency. The 2023 annual quality review of the air conditioning system for a clean area was inspected.

***Nitrogen***

Nitrogen was sourced either from a commercialized supplier or in-house manufacturing according to the "SMP of Nitrogen System in Plant".

**4. Process equipment**

Equipment used in the manufacture of intermediates and APIs was of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization, and maintenance. Equipment was constructed so that surfaces that contact raw materials, intermediates, or APIs did not alter the quality of the intermediates. Permanently installed processing lines were appropriately identified. Schedules and procedures were established for the maintenance of equipment. Records of maintenance and calibrations were maintained and retained following the equipment retirement.

Equipment maintenance and management was handled as per SMP "Equipment preventive maintenance management". A preventative maintenance plan was drafted by the engineering department and approved by QA. The preventive maintenance record for a reactor was verified and found compliant.

Written procedures were established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Equipment and utensils were cleaned, stored, and sanitized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API. Equipment was identified as to its contents and its cleanliness status.

Control, weighing, measuring, monitoring, and test equipment were calibrated according to written procedures and an established schedule. Equipment calibrations were performed using standards traceable to certified standards. Calibration/maintenance schedules for laboratory equipment/instruments and production equipment/instruments were available.

GMP-related computerized systems were validated. Sufficient controls were in place to prevent unauthorized access or changes to data.

**5. Documentation and records**

Documents related to the manufacture of intermediates or APIs were prepared, reviewed, approved, and distributed by QA according to "SMP GMP documentation management procedure". The issuance, revision, superseding, and withdrawal of all documents were controlled with maintenance of revision histories. The control of records was described in "SMP of Record Control Management". Procedures were established for retaining documents, and retention periods for documents were specified.

**Batch numbering and BMR management**

Issue of Batch Manufacturing Records was addressed by "SMP of Code system management". A batch reprocessed/reworked was referenced in the batch number. It was noted that QA was not responsible for the issue of a BMR or Batch Number. BMRs were printed by Production and a batch number was allocated by Production.

**Batch analysis record management**

Specifications of raw materials, intermediates, and final products were documented. It was noted that blank batch analytical documents were issued by QA and used in QC testing. The analysis number (AR no.) allocation, the batch analysis traceability, and history were checked and discussed.

**6. Materials management**

The SOP "Warehousing and distribution of materials" described the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials was available. Incoming starting materials and finished API products were quarantined after receipt until released for use or distribution. The status of raw material was indicated, with respect to material under quarantine, approved, and retest etc. Starting material, packaging material, and finished API products were stored in different warehouses under the specified conditions. A secured area for return and rejected materials was in place. The starting material and finished goods were managed by a manual system.

The following warehouses were visited during the inspection, the warehouses and tank farm were seen to be clean and in good order at the time of the visit.

- Chemical/starting material warehouse
- The sampling area in the solid raw material warehouse.
- Tank farm
- Finished products warehouse

***Supplier Qualification***

The SMP "Material supplier management procedure" for evaluating the suppliers of critical materials was available. Changing the source of supply of critical raw materials was done according to the Change Control procedure. Audits of material suppliers were periodically performed. The audit plan checked was available.

**7. Production and in-process controls**

The facilities and equipment were used for manufacturing of multiple products. API purification, crystallization and drying were performed using non-dedicated equipment in the clean area of a production block. The production areas visited were found to be of suitable standard, clean, and logically organized to suit its intended purpose. During the inspection, Levofloxacin API batches were in manufacturing.

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

Written procedures describing the receipt testing and release and handling of packaging and labelling materials were available. SOP "Label management procedure" and SOP "Product packaging and labeling procedure" were verified. Line clearance was done before and after labelling/packaging procedures. Containers provided adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage. There was no packaging/labeling at the time of the inspection.

## 8. Storage and distribution

*Finished Product Warehouse:*
The finished product storage area was temperature and humidity controlled as per SOP "Receiving & Distribution for Final Products". Printed Packaging components (primary container label) were stored in the Label room in the Finished Product warehouse. Labels for each product were stored in different lockable cages. All printing was conducted by QA with the printed labels returned to the warehouse for manual labelling.

APIs and intermediates were released for distribution to third parties after they had been released by the quality unit and transported in a manner that did not adversely affect their quality. A system was in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

## 10.Laboratory controls

The QC laboratory included the physicochemical laboratory and microbiological laboratory. For the physicochemical laboratory, an analytical competency and analyst signature list was available.

***Physicochemical laboratory***
Separate storage rooms for GC, HPLC, retention samples, stability chambers, and reference standards were available. The laboratory was equipped with personnel, facilities, and equipment suitable for the nature of products and scale of production. The laboratory was responsible for sampling each batch of raw materials, final products according to the procedure requirements and conducting laboratory tests to determine whether they met the specifications, and the issue of an Analysis Report. Sampling for IPQC testing was conducted by production. Samples were received and recorded in a sample register.

The laboratory was established in 2017 and recently upgraded with adequate quality control facilities provided. Procedures were in place describing sampling, testing, approval, or rejection of materials and recording and storage of laboratory data. Specifications, sampling plans and test procedures were available. Sampling and testing of each raw material consignment were performed by quality control as per the sampling plan. Laboratory controls were followed and documented at the time of performance. Any departures from procedures were documented and explained. Laboratory tests were performed for each batch of intermediate and API. Batch release and issue of in-house CoA. The certificates of Analysis were verified. Confirmation that tests complied with specifications.

***OOS***
OOS results obtained were investigated and documented according to the SMP "OOS/OOT/OOE Investigation". A laboratory investigation form was completed. OOS results derived during stability studies could result in a recall of the product. OOS results are added to the APQR. Overall annual trending is available as per the log register. For 2023, no OOS results were obtained for any of the WHO products.

**Stability studies**
A documented stability testing programme was in place. Test procedures used in stability testing were validated. Stability samples were stored in packaging that simulated the market container. At least one batch per year of API manufactured was added to the stability monitoring programme and tested. API expiry or retest date was based on an evaluation of data derived from stability studies. Various stability chambers were available in the stability room. Stability testing was driven by QA as per the "Stability sample instruction sheet". As from February 2024, a stability monthly testing plan was introduced. The procedure for conducting stability studies was inspected. The stability report for a Levofloxacin batch was verified.

***Reference Standards***

Reagents prepared in the laboratory were prepared and labelled following written procedures with an allocation of an expiry date.

Primary reference standards were available. Records were maintained of each primary reference standard. Working reference standards (WS) were appropriately prepared, identified, tested, approved, and stored.

***Retention samples***

Reserve samples of each batch of API were retained for one year after the expiry date, or for three years after distribution of the batch, whichever is longer. Enough reserve samples were stored in the same packaging system in which the API was stored.

***Laboratory equipment***

All laboratory equipment had usage and calibration logbooks. The following laboratory equipment was checked:

- Balance. Daily weight verification checks prior to use were performed. Weight calibration certification was available.
- HPLC. Usage log and maintenance log were verified. Column used with corresponding logbook available.

***Microbiology Laboratory***

The microbiological laboratory was separated from the physicochemical laboratory. The laboratory was briefly visited. The "SMP of medium" and PW sample register for TAMC testing were verified. The Annual Review (2023) for the Purified Water was verified, and the data was within the specification limit.

**11.Validation**

The Qualification and Validation policy of the site was described in an approved "Validation Master Plan".

***Process validation***

Process validation was addressed in "SMP of Manufacturing Process Validation". Validation data for the manufacture of Levofloxacin was verified. The following process validation documents for Levofloxacin were checked.

**Cleaning Validation**

Cleaning validation was addressed in "Cleaning validation management procedure". The cleaning validation protocol and report for Levofloxacin documents were checked.

**Computerised system validation**

Computerized systems were used in the QC Lab with software programmes. The validation for the computerised systems was not checked in detail due to time constraints.

**12. Change control (CC)**

Change control to evaluate changes that may affect the production and control of intermediates or APIs was addressed by a written procedure. Changes were classified into three classes as well as permanent and temporary change. The potential impact of the proposed change on the quality of the intermediate, or API was evaluated. Timelines for implementation, closure, and assessment were established. The 2023 CC register was available and verified. The change controls related to Levofloxacin production were checked.

**13. Rejection and re-use of materials**

Rejected material was handling following the SMP "Rejected material control management". All records were maintained in the quality assurance department.

**Reprocessing and Reworks**

Reprocess and rework were described in the "SMP of reprocessing and reworking management procedure". There were no reprocessing batches reported for the WHO grade of Levofloxacin API.

**Recovery of Solvents**

The SMP "Recovered solvent management procedure" was verified. No external contractors were used for solvent recovery.

## 14. Complaints and recalls

***Complaints and recalls***

Quality related complaints were recorded and investigated according to the "SMP of complaint". The QA Department coordinated a root cause/most probable cause investigation and impact assessment of the complaint, proposed investigation into related products and established corrective and preventive measures. The investigation results of a customer complaint were communicated to the complainant within a prescribed timeline. If necessary, a recall of the product may be initiated. Records of complaints were retained to evaluate trends, product-related frequencies, and possible recall of products from the market. CAPA that originated from complaints were handled according to "SMP of corrective and Preventative Actions". If the product needed to be returned, the matter was handled according to "SMP of Returns". Complaints were recorded on a complaint handling form.

***Recalls***

Handling of recalls was described in the "SMP of recall". Recalls were divided into first level recall, second level recall and third level recall, with each level having a different requirement for timelines. QA was responsible for making the recall decision and for coordinating all relevant actions. Reporting to the local authorities was done by QA. The classification was according to health impact and urgency. In the event of a serious or potentially life-threatening situation, local, national, and international authorities were informed.

To evaluate the efficacy of the SOP, a mock recall was performed yearly. The latest mock recall classified as a Second level recall and performed in 2023 was checked and discussed.

## 15.Contract manufacturers (including laboratories)

Quality agreements were checked. The contract acceptor and contract giver responsibilities were clearly defined. Contract analysis was described in the "SMP of contract lab". An approved list of contract laboratories was in place.

| 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, ***Zhejiang Langhua Pharmaceutical Co., Ltd***, located at ***No.7, Donghai 3rd Avenue, Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone, Linhai, Zhejiang, P.R. China*** 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 |
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1. 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***
   untitled (digicollections.net)

2. 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://digicollections.net/medicinedocs/documents/s21467en/s21467en.pdf

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   ***Short name: WHO TRS No. 1033, Annex 3***
   9789240020900-eng.pdf (who.int)

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   ***Short name: WHO TRS No. 929, Annex 4***
   https://digicollections.net/medicinedocs/documents/s21440en/s21440en.pdf

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
   https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1010-annex8-who-gmp-heating-ventilation-airconditioning.pdf?sfvrsn=c77698e2_0

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4.
   ***Short name: WHO TRS No. 937, Annex 4***
   https://digicollections.net/medicinedocs/documents/s20108en/s20108en.pdf

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report, Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 4.
   ***Short name: WHO GPPQCL Guidelines, TRS No 1052, Annex 4***
   https://www.who.int/publications/i/item/9789240091030

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
   ***Short name: WHO TRS No. 957, Annex 3***

https://digicollections.net/medicinedocs/documents/s22358en/s22358en.pdf

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.
***Short name: WHO TRS No. 961, Annex 6***
https://digicollections.net/medicinedocs/documents/s19959en/s19959en.pdf

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

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. ***Short name: WHO TRS No. 961, Annex 9***
https://digicollections.net/medicinedocs/documents/s18683en/s18683en.pdf

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://digicollections.net/medicinedocs/#d/s21438en

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://digicollections.net/medicinedocs/documents/s18682en/s18682en.pdf

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://digicollections.net/medicinedocs/#d/s20177en/

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://digicollections.net/medicinedocs/#d/s20175en/

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***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***
https://digicollections.net/medicinedocs/documents/s23697en/s23697en.pdf

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

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

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

21. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS No. 1033, Annex 4***
TRS 1033 - Annex 4: WHO Guideline on data integrity

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

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
***Short name: WHO TRS No. 1010, Annex 10***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditionning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
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25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. **Short name: WHO TRS No. 1033, Annex 2**
9789240020900-eng.pdf (who.int)

26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. **Short name: WHO TRS No. 1025, Annex 6**
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27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***
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28. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. Short name: WHO TRS No. 1025, Annex 4
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29. WHO good manufacturing practices for excipients used in pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 2. ***Short name, WHO TRS No. 1052, Annex 2***
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