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Prequalification Team Inspection services
WHO INSPECTION REPORT
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Beximco Pharmaceutical Limited
Corporate address of manufacturer	19 Dhanmondi R/A, Road No: 7, Dhaka-1205, Bangladesh
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Track-2, OSD Facility, 126, Kathaldia, Auchpara, Tongi-1711, Gazipur, Bangladesh
Unit / block / workshop number	OSD Unit (Track-2, in short T-2)
Manufacturing license number	License No. 119 and License No. 379
Inspection details	
Dates of inspection	15 to 18 May 2023
Type of inspection	Routine re-inspection
Introduction	
Brief description of the manufacturing activities	Production and quality control of OSD (tablets and capsules) and inhaler products is performed on-site but only OSDs were in WHO PQ scope.
General information about the company and site	Beximco Pharmaceutical Limited is a public limited company established in 1976. The company has four manufacturing sites and one R&D set-up. Out of four manufacturing sites, three manufacturing sections and R&D are located at the site at Tongi, Gazipur, Bangladesh, approximately 25 km north of Dhaka city. The three manufacturing sections managing operations on the Tongi site are referred to in the company as Track 1, Track 2 and Unit-3. Each track is functionally independent and has its own senior management group, with its own manufacturing facilities and laboratories.

	The section responsible for the product within the inspection scope (HA 668 Lamivudine Film-coated Tablets 300mg), Track 2, has five units: OSD unit, MDI unit-I, MDI unit-2, MDI unit-3 (Under commissioning) and DPI. The company declared that some of its other FPP products including penicillin and cephalosporin products, were also managed by the Track 1 Section. The company stated that the penicillin facility is located on a separate site at Kaliakoir, 21 km from the Track-2 operations at Tongi, Gazipur, and it is the only group management for the antibiotics that resides at Tongi. The company stated that Cephalosporin products were manufactured by third parties via CMO contracts. No non-therapeutic products, veterinary products, food, cosmetics, insecticides, herbicides and animal poisons are manufactured in Beximco Pharma facilities at Tongi, and no toxic substances, hormones, immunosuppressants, steroids, vaccines, biological agents, gases and cytotoxins are handled at this site.
History	This was the third WHO inspection of the site with the last inspection performed on 10 to 12 March 2020.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	• Quality management system • OSD production block, Track 2 • Warehouses of Track 2 • QC including chemical and microbiological laboratories • Stability study area • FG sample retention area
Restrictions	The inspection was restricted to the production of the product listed in the inspection scope.
Out of scope	Products and production areas outside of the inspection scope were not inspected.
WHO products numbers covered by the inspection	HA 668 Lamivudine Film-coated Tablets 300mg
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CMO	Contract manufacturing organization
CoA	Certificate of analysis

CpK	Process capability
DMS	Document management system
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RPN	Risk priority number
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file

SOP	Standard operating procedure
TAMC	Total aerobic microbial count
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

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

1. Pharmaceutical quality system

A documented system for quality assurance was established, with procedures covering key quality elements in place. 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. The procedures reviewed and discussed during the inspection were generally of an acceptable standard.

Annual Product Quality Review

The company had in place a procedure for performing product quality reviews. APQRs are performed annually for the period January to December. The SOP as a general description for APQR was in place and included the purpose, scope, responsibility and procedure. It allows for APQR to combine two review periods in the case of a limited number of batches. The updated SOP stated the role and QA's responsibility.

The last inspection reviewed the APQRs up to the end of 2019 and the situation has been unchanged since that time as there had been no production, stability batches or process revalidations performed since 2016, nor had there been any commercial sale of Lamivudine Film-coated Tablets 300mg. The original validation lots were destroyed in 2019. The company also had available APQRs for the last three years 2020, 2021 and 2022 however the available APR documents were therefore very restricted in content and were basically a development and validation history of the PQ'd product to date, reporting on the results of the terminated long term ongoing stability monitoring (extended to 4 years) of the original dossier submission lots.

Although the company was fully aware that process revalidation and further commercial lot stability testing would be necessary should there be commercial orders for Lamivudine Film-coated Tablets 300mg, there was no discussion of these future requirements in the 2022 PQR.

Quality Risk Management

Quality risk was managed according to a written procedure which was reviewed. Risk management was managed with the computerised system "MASTERCONTROL" from March 2023.
An annual review report of quality risk assessment for T2 in 2022 was in place. The risk assessment for the newly introduced computerised system "MASTERCONTROL" was checked and found generally acceptable.

Management review (MR)

Management review followed a written procedure which was reviewed. It required MR to be performed twice a year with the attendance of senior management. The report for the MR meeting held in February 2023 for the period of January to December 2022 was reviewed. The information on key elements of QMS was reviewed and documented.

Deviations

The company had a procedure for deviation management. The procedure defined what a deviation is, being planned or unplanned and three classification levels, critical, major and minor based on the impact analysis. The procedure also allows for immediate action that can be initiated. Upon a deviation event, the deviation report form is completed. Risk assessment was logged and the setup of a cross-functional team for the root cause investigation was launched. Closing CAPA resulting from deviation should be completed within specified days. Extending the closure date requires justification.

There were no deviations relevant to the production process or equipment of Lamivudine Film-coated Tablets. Example deviations for other products were examined and found satisfactory without comment.

OOS/OOT management

A procedure for handling OOS was available and reviewed. OOS/OOT was managed with the computerised system "Mastercontrol". The OOS investigation was spot-checked in this computerised system and the investigation history was available. There was no OOS/OOT for Lamivudine Film-coated Tablets 300mg as there were no batches produced since it's qualified by PQ programme.

CAPA:

The company established a procedure for handling deviations, OOS and non-compliance. CAPA was registered and managed with the computerised system "Mastercontrol".

Change Control

Adequate change control procedures were in place and linked to the QRM and new product introduction SOPs. The company now registers and manages changes with the computerised system "Mastercontrol".

The most significant change in the last six months has been the first phase of the implementation of the aforementioned computerised system "Mastercontrol". The software was discussed in some detail. The "go live date for the modules implemented was within the last two months before the inspection and currently, the company is restricting write access and workflow tasks to a relatively small number of super users.

The company has also recently acquired an automated tablet inspection machine and is undertaking validations for products manufactured currently. Protocols were discussed but no reports are currently available as work is ongoing.

Product Release

Product release was managed according to the final product release procedure. QA was responsible for the final review of all the relevant documents including BMR, BPR and batch testing records for the release finished product according to the SOP. No commercial batches of Lamivudine Film-coated Tablets 300mg have been released to supply to market yet.

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 maintained at a satisfactory level of cleanliness at the time of inspection. Personal hygiene and sanitation appeared satisfactory. Areas were cleaned frequently in accordance with an approved written programme. Personnel at the site were seen to be performing their duties in an organized and diligent manner.

4. Qualification and validation

Validation master plan

An approved VMP was available and reviewed. The company qualification and validation policy and programme were defined and documented.

Process validation

Process validation was performed according to the in-house validation procedure. The process validation of HA 668 Lamivudine Film-coated Tablets 300mg was performed in 2017 with three batches. The process validation protocol and report and BMRs of PV batches were reviewed in the last inspection. There was no new validation for Lamivudine performed since the last inspection.

Equipment qualification

The equipment qualification procedure was available for review. A new tablet inspection machine was introduced since the last inspection. PQ for the automatic inspection machine approved in November 2022 was reviewed and discussed.

Cleaning validation

The current cleaning validation report dated July 2022 was reviewed. The approach to cleaning validation mentioned in VMP was acceptable.

Computerised System (CS) validation

Computerized systems were used in the following activities.

- Inventory
- Production All PLC-based Equipment
- Engineering BMS for HVAC & SCADA for Water System
- Track and Trace system Serialization from primary bottles to palletization (Aggregation)
- QMS & DMS (Mastercontrol)
- FBS (Field Based Solutions) Modules like Management of Change, Deviation, Complaint, Event Report, Non-Conformance, OOS/OOT, Issue review and Meeting Minutes have been implemented.
- Equipment Calibration, Equipment Maintenance (Corrective and Preventive), Audit, Training and Supplier Module will be implemented in phase-2 (Tentative Time: September 2023)

The computerised system "Mastercontrol" was reviewed and mentioned above in the change control section of this report.

5. Complaints

Product quality complaints were handled according to a written procedure which was reviewed. The complaints were classified into class tiers 1 and 2 as well as categorised into critical, major and minor. It was the responsibility of QA to investigate complaints and implement CAPA if necessary. No complaints on Lamivudine Film-coated Tablets 300mg tablets were received as there was no commercial batches have been manufactured since it's prequalified by WHO.

6. Product recalls

Product recalls were handled according to a written procedure which was reviewed. The recall was classified as a Class I, Class II or Class III defect, and the action is required to be initiated within the specified time. The WHO PQed Lamivudine Film-coated Tablets 300mg tablets have not been supplied to markets. No batch has been recalled.
Recall simulation was required to be performed for both domestic and export markets if no real recall occurred. A mock recall performed in September 2021 for a tablet product for the export market was reviewed.

7. Contract production, analysis and other activities

The production for the WHO PQ FPP Lamivudine Film-coated Tablets 300mg tablets in the inspection scope was not contracted.

Several contract labs are used for the following testing. The qualification requirements for contract laboratory service were checked.

- N-Nitroso dimethylamine (NDMA) content by LC-MS/MS
- N-Nitroso dimethylamine (NDMA) content by LC-HRMS
- Nitrosamines impurities by LC-MS/MS
- Elemental Impurities by ICP-MS
- Lead content by ICP-MS
- Identification by XRD

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

Self- Inspection

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

Supplier qualification and approval

The supplier qualification and approval were managed according to a written procedure which was reviewed. The scope of suppliers covered all starting materials, analytical and calibration services, as well as the vendors providing application and computer system validation services. The quality agreement with the supplier of the Lamivudine API was reviewed.

9. Personnel

An organization chart was available. Key personnel responsibilities were required to be defined in job descriptions. The key personnel of the various departments had pharmaceutical qualifications and were well-experienced in pharmaceutical manufacturing.

The Company employed 363 professionals and 632 operators at the time of the inspection. Of them, 516 staff members were engaged with Track 2 manufacturing according to the company presentation at the time of inspection. The number of personnel appeared adequate to the present activities. In general, personnel met during the inspection are aware of and follow the GMP principles with appropriate qualifications and experience.

10. Training

QA was responsible for the training of personnel. Training was required for newly appointed and job-specific training and re-training in the event of personnel errors, resulting in a CAPA event. A training programme was not reviewed in detail. The effectiveness of training was evaluated during inspection e.g., equipment cleaning.

11. Personal hygiene

Personnel hygiene requirements were documented in written procedures. The requirements for entry Grade D cleanrooms were well documented, including pictorial drawings in change rooms. Staff observed in these areas were dressed in appropriate protective clothing.

12. Premises

Track 2 OSD facility is multi-product and not dedicated. Manufacturing areas were of a good 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 application of cleaning. The classified areas were monitored for temperature, relative humidity and pressure differentials with a BMS system for environmental control.

QC laboratories were separated from production areas. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. The retention samples room and stability chambers were located in two different buildings from the QC laboratories.

Utilities

Adequate ventilation, air filtration and exhaust systems were provided. The HVAC system providing filtered air to the Grade D cleanrooms was spot-checked. The procedure for the Operation of the air handling Unit (AHU) was reviewed.

Purified water

Purified water was produced from bore well water by single RO followed by EDI. A water system was briefly visited. The P & ID of the PW system was in place. The distribution loop was sanitized routinely at specified intervals.
The annual review report of the water system for OSD Track 2 for the period of January to December 2022 and the SOP for sampling and testing of PW were reviewed. The alert limit and action limit of TAMC were specified. Sampling and testing for PW microbiological limit were reviewed and discussed.

Lighting

Lighting was adequate in all areas visited during the inspection.

Sanitation and maintenance

All areas visited appeared to be clean. There was evidence of suitable pest control measures throughout the premises.

13. Equipment

Equipment installed in the production block Track 2 was multi-purpose and each piece of equipment had a unique identification number. The equipment viewed appeared to be of suitable design and construction for the allocated process in general.

Equipment maintenance and cleaning

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

The equipment preventive maintenance was managed according to a written procedure. The preventive maintenance schedule was required to be prepared for a year in two halves. The maintenance schedule for January to June 2023 was available for review.

Equipment cleaning

In general, the production facilities were well maintained, and the equipment were free of any dust and residues. Almost all transfers are using closed equipment.

14. Materials Management

Incoming materials and finished 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 retested etc. The starting material and finished goods were managed by the ERP system.

Starting material, packaging material and FPPs were stored in different warehouses under the specified conditions. The warehouses were visited during the inspection. The codes and locations for starting material and finished goods were spot-checked in the ERP system.

The raw material warehouse was equipped with two sampling booths under LAF with separate entrances for materials and personnel. The sampling procedure for raw materials and the sampling and cleaning logbook were checked. A secured area for return and rejected materials was in place.

Lamivudine tablets validation batches with 24 months shelf life had expired and no batches were stored in the warehouse.

15. Documentation

Documentation was designed, prepared, reviewed and distributed according to an approved procedure. Computerised systems "Mastercontrol" and FBS (Field Based Solutions) were used for QMS and DMS.

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products.

Batch numbering system and BMR management

The procedures for product batch numbering and management and for issuance of working copies of batch production records and analytical worksheets using mater control were reviewed. The authorized master formulae were available for commercialised products. Batch manufacturing records (BMRs) were retained for each batch processed. The management regarding batch cancellation was discussed.

16. Good practices in production

The manufacturing processes were performed and recorded according to instructions in the batch production records. The production of Lamivudine tablets has not been performed since it was PQed in 2017.

Because of the lack of recent production experience, a full risk-based review/revalidation should be performed if a commercial batch is to be produced by the company.

Production of several tablets other than Lamivudine tablets was in operation at the time of inspection. Tablet's manufacturing steps including material dispensing, granulation, compression, coating and primary, and secondary packaging areas and finished product storage rooms in Track 2 were inspected. Manufacturing records of the products under production were spot-checked and found acceptable.

In-process control was conducted at several IPC laboratory spots inside of the Track 2 production block. Appropriate testing equipment was available.

Reprocessing was allowed for the domestic market but not for international supply. The procedure for reprocessing products for the domestic market was reviewed and discussed. Reworking is not acceptable for any market.

17. Good practices in quality control

The QC function was independent of other departments. QC laboratories of OSD Track 2 were separated from production areas. It was housed across two floors including a microbiological laboratory. The microbiology laboratory was segregated from the chemistry laboratory.

Sample receiving and distribution

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

Testing of starting material and finished products

The procedure for testing and release of raw material and the procedure for bulk and finished product release procedures were reviewed.

Finished product release testing for tablets was performed with bulk tablets before primary packaging and not on the final finished product. QC subsequently, after primary and secondary packaging, testing only for the Packaging QC.

Retention samples

Retention and retained samples were kept in a secured and temperature-controlled (below 25^0C) room. The retention sample register and samples of each batch were kept. An annual check for the sample was performed according to the company procedure.

Stability study

Satisfactory SOPs were in place. As noted above, there were listed four product codes for lamivudine tablets 300mg. The WHO Lamivudine tablets 300 mg batches for process validation were produced in 2017 and when these studies were terminated there was no ongoing stability due to the lack of production.

In view of the time that has passed since prequalification a full risk-based review and product transfer to commercialisation should be considered prior to the release of any commercial lots.

Instrumentation

The company has adequate numbers of instruments and equipment for QC laboratories. The records and logs are adequately maintained. Status labels were attached to equipment and found acceptable. Calibration status and dates were acceptable. QC chromatographic analysis was operated and controlled with Empower 3 software with real-time transfer.

Microbiology Laboratory

The microbiological laboratory was adequately equipped and appeared to be of an acceptable standard for non-sterile products. Media preparation and sterilization procedures and records were reviewed. PW testing procedure, records and monitoring results for microbiological limit were spot-checked. The monitoring results appeared acceptable.

Part 3	**Initial conclusion – Inspection outcome**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, ***Beximco Pharmaceutical Limited,*** located at ***Track-2, 126, Kathaldia, Auchpara, Tongi-1711, Gazipur, Bangladesh*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

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

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

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

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
   https://digicollections.net/medicinedocs/documents/s21467en/s21467en.pdf

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***
   untitled (digicollections.net)

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. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1.
Short name: WHO TRS No. 961, 957), Annex 1
https://digicollections.net/medicinedocs/documents/s18681en/s18681en.pdf

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***
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13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2.
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. Fiftieth 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-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://digicollections.net/medicinedocs/documents/s23699en/s23699en.pdf

25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. **Short name: WHO TRS No. 1033, Annex 2**
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26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. **Short name: WHO TRS No. 1025, Annex 6**
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27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***
https://www.who.int/publications-detail/978-92-4-000182-4

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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