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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Calyx Chemicals & Pharmaceuticals Ltd
Corporate address of manufacturer	Unit No.110, Marwah's Complex, Krishanlal Marwah Marg, Off. Saki-Vihar Road, Andheri (East), Mumbai- 400 072. Maharashtra, India. Tel: +91-22- 28571190/ 28571191/66077500, Fax: +91-22-66466416, E-mail: calyx@calyxindia.com D&B D-U-N-S Numbers: 65-042-7912 GPS Coordinates: Latitude:-19.78810 Longitude:-72.72200
Inspected site	
Name & address of inspected manufacturing site if different from that given above	N-102, 91&90, MIDC, Tarapur, 401 506 District Palghar, Maharashtra, India Plot No. N/102, 91 & 90, MIDC, Behind Vadilal Ice cream, Tarapur, Boisar. Dist. Palghar (Maharashtra), India, Pin Code-401 506 Tel. No:+91–2525-274020/645617/645975/645976 Fax No.: +91–22-66466426
Synthetic unit /Block/ Workshop	Plants I, II, III, IV, V
Inspection details	
Dates of inspection	28 January to 01 February 2019
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	Production of APIs and API intermediates. The APIs manufactured: For WHO (not exclusively): pyrazinamide (Plant I/II), Isonicotinamide for isoniazid (Plant III), isoniazid (Plant I/II), dihydroartemisinin for artemether (Plant III). artemether (Plant IV), DDFE for lumefantrine (Plant III, VI1), lumefantrine (Plant I/II/V). Not for WHO: erythromycin, flucytosine, zopiclone, cetirizine dihydrochloride, erythromycin stearate, erythromycin ethyl-succinate. The recent version of the SMF: SMF/QA/05, 09/01/2019
General information about the company and site	The company was founded in 1979. The manufacturing site is located at Tarapur, ca. 110km north of Mumbai, in Maharashtra State. It was commissioned in 1998. At the time of the inspection there were 203 permanent and 11 temporary staff. There are eight production plants. No

	high-potency materials etc are manufactured on the site. The Company has a manufacturing and development site in Dombivili, India, which has stopped manufacturing activities 5 years ago. The company is currently managed by a Resolution Professional with support from Calyx management. New investors have been identified and will be in place from the following financial year, April 2019.
History	The regulatory inspections at the site: - 2003 December (WHO Geneva) - 2009 September (Korean FDA) - 2009 September (WHO Geneva) - 2009 December (USFDA) - 2012 February (EDQM) - 2012 March (USFDA) - 2012 March (WHO Geneva) - 2014 December (CDSCO) - 2016 March (USFDA) - 2017 August (WHO Geneva) - 2017 February (CDSCO) There were no substantial changes made in terms of instrumentation, facilities, product line, manufacturing processes, and analytical instrumentation since the last WHO inspection.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	General overview of the CAPA's and remediation measures made to address the observations of the last WHO inspection. o Product Quality Reviews o Change Control o CAPA management o Change Control o Reprocess-rework o Vendor qualification o Risk management o Deviation management o Recalls o Batch manufacturing records o Calibration and qualification including process equipment, HVAC and PW system o Organizational chart and job descriptions o Training, personnel hygiene, gowning, o Rodent and pest control o Material management, including warehouse tour o Production, including tour at the manufacturing facilities o Quality control

	o Stability program (including tour at stability chambers) o Reference sample storage (tour
Restrictions	None
Out of scope	Only WHO APIs were covered
WHO APIs covered by the inspection	APIMF078 Pyrazinamide APIMF086 Isoniazid APIMF120 Artemether APIMF121 Lumefantrine

Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
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	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance

PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

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

1. Quality management

Quality unit has the overall responsibility for improving the quality systems, procedures, standards, implementation of cGMP and to maintain the quality of the products. The quality unit is independent of production. The quality unit is responsible for different aspects related to the quality systems, not limited to the following:

- Approval or rejection of all raw materials, intermediates, API's.
- Reviewing and approving of quality specifications, test methods, completed batch production records, laboratory control records, validation reports, protocols and approval of changes that can impact quality.
- Stability program (stability data available to support retest/expiry dates, storage conditions, reports etc.),
- Supplier qualification,
- Management of regulatory and customer inspections,
- Internal quality audits,
- Managing and decision on investigations (CAPAs, change controls, deviations, customer complaints),
- Maintenance and calibration program,
- GMP training.
- Product recalls
- Compilation of PQRs.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Personnel

Training procedure was reviewed. Training was basically divided into internal and external training wherein internal training was further divided into induction training, orientation training, on the job training, ongoing training and refresher training. Evaluation criteria was set using questionnaire with not less than 80% acceptance criteria. A certificate was issued following the successful completion of the training. The human resource department prepares the annual training schedule. In general, the procedure appears detailed enough and satisfactory.

Annual training schedule for the year 2019 was available which listed several topics for training. Some of the topics covered for 2019 include: personnel hygiene, process validation, cleaning of small accessories, entry/exit of employees into production area, ICH Q7, cleaning validation, reporting / recording deviations, basic GMP, BMR writing, qualification of equipment, good documentation practices, reprocessing, reworking, quality risk management and corrective and preventive actions. It appeared that training of data integrity and self-inspection was not part of the 2019 program. The data integrity training was limited to QA/QC personnel without any justification.

A separate procedure for contract labour management was in place. The human resource and administration department are responsible for ensuing compliance with this procedure. These contractual workers are recruited for cleaning and housekeeping of the plant area including loading / unloading of materials. Medical check-up was limited to those workers who can read and write and competent enough to work in clean room area. The contractual workers go through induction training which included training on personal hygiene, training on GMP and training on safety.

The gowning rules and the entry/exit rules of the production areas were stated in the procedure supported by a garment colour coding system. In level III (clean areas) operators and executives wear light blue colour with staff changing garments daily which is washed by two contract laundries (daily service).

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Buildings and facilities

The company layout was approved by the local FDA on 15/07/17.

Cleaning procedures were reviewed. In general, these procedures were found adequate except minor comments. Product changeover cleaning was performed after every product changeover and campaign. The cleaning validation system was revised since the last inspection. The following product changeover cleaning validation protocols and reports were discussed:

The pest and rodent control was managed by a contract partner based on SOP and a contract by means of

- Roda boxes (48 pcs),
- Gold seal service,
- Insect traps
- Integrated spider control
- Prophylactic treatment,
- Integrated lizard management,
- Integrated fly management.

Rodent boxes with bromadiolone containing cakes were placed outside of the buildings. No chemical protection was applied inside the warehousing and production areas.

The qualification and maintenance program with the corresponding records of the AHU1 (supplying CF room of Plant I) were discussed. The qualification and maintenance program did not change since the last WHO inspection.

Purified water system did not change since the last inspection. The water testing protocol and the recent result of sampling point SP10 (located in Plant 2, crystallization area), every 15 days on Wednesday were discussed. The sampling and testing records were available. Sampling and testing schedule of purified water, demineralized water and potable water.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

4. Process equipment

The process equipment did not change since the last WHO inspection. There was a qualification program in place for process equipment. The qualification protocol and records of CF-01 were discussed.

Preventive maintenance (PM) was assured by means of equipment specific PM protocols and an annual PM planner for equipment. The maintenance schedule for Plant I/II/III was available and discussed. The maintenance of SS reactor was performed according to protocol.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

5. Documentation and records

The master list of SOPs was available.

The batch manufacturing record masters applicable for WHO products were as follows:

BMR/108	06	14/12/2017	Pyrazinamide	PI-II
BMR/107	04	23/072015	Pyrazinamide Blending of tailing material (for WHO)/ blending of recovered material (not for WHO)	PI-II
BMR/1402	17	14/02/2018	Isoniazid stage-I (Isonicotinic acid amide)	P-III
BMR/1403	11	14/02/2018	Isoniazid Final Stage	P-I, II
BMR/1416	02	01/12/2017	Isoniazid Purification	P-I, II
BMR/1223	03	20/12/2017	Dihydroartemisinin	P-III
BMR/1961	03	15/12/2017	Artemether Crude	P-III
BMR/1962	04	08/12/2017	Artemether Final Stage	P-IV
BMR/2419	00	26/07/2016	Epoxide to DDFE	P-III
BMR/2420	01	20/12/2017	Epoxide to DDFE	P-II
BMR/2417	04	16/12/2017	Epoxide to DDFE	P-VI
BMR/2421	00	16/12/2017	Epoxide to DDFE	P-V
BMR/2670	07	04/01/2019	Lumefantrine (Epoxide Route)	P-V
BMR/2718	00	18/12/2017	Lumefantrine (Epoxide Route)	P-VI
BMR/2719	00	20/01/2018	Lumefantrine Purification	P-I-II
BMR/2717	00	09/12/2017	Lumefantrine (Reprocess)	P-V

The SOP for SOP management & document control was discussed. The SOP described the procedure as to how documents are handled at Calyx. In addition, the procedure described the preparation of master batch records, batch manufacturing records (BMR), validation protocols and handling of copies for regular use. The BMRs are archived for a period of 6 years. Similarly, records generated by the laboratory are archived for 6 years. It was noted that all validation documents, annual maintenance contracts, drug master files, and master formulas are archived for a lifetime.

The retention period of obsolete copies is retained for a period of 5 years. The SOPs are revised once every three years if there are no changes required. A stamp was put on those SOPs as “Reviewed & Revalidated” which did not require revision. The procedure was supported by several annexures. It was however noted that this document control procedure does not provide any information and requirement for the handling of data/records generated from the electronic systems.

The BMR issuance register for each API was maintained which captured details of the issuance date, issuance number, batch number, BMR number & revision number, issued by and received by. Issuance of master batch manufacturing record register for 2017 to 2019 was reviewed. The register provided details of plant number, BMR number, BMR revision number, approval date, and effective date, BMR issued and withdrawn.

A common BMR for the micronization stage was in place. It was noted that no micronization was performed for Pyrazinamide and Isoniazid whereas Lumefantrine and Artemether are micronized. The BMR identified two micronizers (MZ-1 and MZ-2) and micronization parameters (air pressure for feed chamber and jet chamber and feed rate), which differs from molecule to molecule and recorded in the BMR. After micronization, the product is sent to a laboratory (Centre of Excellence, based in Vapi) for particle size distribution.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections

6. Materials management

The batch numbers were generated based on reflecting the item code of the API/intermediates, the date with a running serial number restarting annually. Irregularities, special features (e.g. R for reprocessing, 0 for blending, N for non-regulated markets, M for micronized, W for reworking) were also indicated.

ERP inventory system was used for material management. It was claimed that unique item codes are being issued to same material with different sources.

The vendor qualification of both the KSMs and non-KSMs was covered in the procedure. The qualification documents (questionnaire, certificates, process flow, CoAs) of vendor were discussed. The vendor related information was gathered from different sources.
The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

7. Production and in-process controls

In 2019, the following batches of WHO PQ products were produced:

Isoniazid	Artemether	Pyrazinamide	Lumefantrine
3 batches	No production	14 fresh batches	13 fresh batches
One CEP grade and two WHO grade	One batch for micronization	2 batches	2 reprocessed

In 2018, the following batches of WHO PQ products were produced

Isoniazid	Artemether	Pyrazinamide	Lumefantrine
3 batches	44 batches	154 batches	156 batches
All reprocessed	All approved	All approved	2 batches

Batch manufacturing record of Lumefantrine (Epoxide route) was reviewed and noted that dispensed labels were attached to the BMR. DDFE is produced in-house and used as an intermediate for the manufacturing of Lumefantrine. The required details were part of the BMR. The in-process tests were performed in the main laboratory as production did not have any in-process laboratory. The in-process tests and complete testing of Lumefantrine were cross-verified and found satisfactory.

The SOP for blending of API & intermediate described that if the recovered material available, it can be blended with tailing/leftover batches to make blend batch and label as Indian Pharmacopoeia to non-PQ customers. A unique batch number was assigned for such blend batches.

Blending procedure was revised and made clear that the same specification material will be blended. Also, the procedure stated that OOS batches will not be blended. On complete testing of a lot before blended, this was also addressed in the revised procedure. The procedure was cross referenced with another procedure "stability study for API and intermediate".

Common synthesis area used for various products, commonly manufactured Pyrazinamide and Isoniazid. The reactors used for the synthesis are non-dedicated. It was claimed that only one substance is produced at a time. Each reactor was identified with status label providing information on previous product and batch number and name of present product and batch number.

Powder processing area of P-II: interlocking was provided between rooms. The area was equipped with three crystallizers (I, II & III) and two centrifuges (I & II). After crystallization, Pyrazinamide was centrifuged in four parts and then dried in three parts and finally milled and blended. It was claimed that dedicated hose pipes are used. Vacuum transfer system was used for the transfer of in-process materials from centrifuge to FBD bowl and then to co-mill and octagonal blender.

The batch manufacturing record of Isoniazid was discussed.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

8. Packaging and identification labelling of APIs and intermediates

The packaging and labelling procedure did not change since the last WHO inspection. The practice was discussed during the site tour at the warehouses.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections

9. Storage and distribution

Inspection of warehouses covered the storage areas used for WHO (details see section 3. Buildings and facilities). The common stock register (maintained manually) used for capturing incoming materials before entering the warehouse. The ERP system was limited to receipt of materials.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

10. Laboratory controls

The wet laboratory was responsible for the receipt and testing of raw materials, in-process samples and finished APIs. Since the last WHO inspection in August 2017, the laboratory confirmed that there were no substantial changes made except three new equipment (UV-VIS from Jasco, KF apparatus and Melting Point apparatus) were purchased and commissioned for daily use.

Sample inventory register, except for raw materials was maintained via *product wise*.

There were no analytical methods validated.

The date/time stamp was found to be locked at the time of the inspection. Unique user ID and password were given to laboratory analysts. Apart from Windows unique ID and password, respective software (e.g. Spectra-Manager for IR) were accessible through unique ID and password. The analytical balances were equipped with printers with date/time stamp locked. The laboratory claimed that the service engineer of the balance provider has locked these balances and they are the only one having access for any modification.

In the instrumental laboratory there were stand-alone workstations operated according to IT rules.

The SOP for review of the audit trail was discussed which provided guidance for the review of audit trail procedure. After completion of the analysis, the reviewer shall review the data using his/her user ID. The system administrator (IT) takes daily backup of an audit trail as well as data files of the critical computer. The procedure was supported with audit trail checklist which was used by both QC and QA to verify the integrity of data.

The SOP for computer access control was reviewed. It described the access control procedure, assigning user registration and user access rights. Currently, the site has only one administrator who is responsible for the creation of user ID, issuance of the password, allocation of access rights, backup of data etc. In general, the procedure appeared satisfactory. An equipment register was maintained for the list of user identification with applicable privileges (operator, method developer, and administrator). The laboratory uses different software for HPLC and GC systems (*LC solution* for Shimadzu HPLC, *Lab Solution* for Shimadzu HPLC, *GC Solution* for Shimadzu GC, *OpenLab* for Agilent GC, *IR solution* for Shimadzu FTIR).

The SOP on backup and retrieval of electronic technical data was reviewed which required day to day electronic data be stored in D drive and then daily manually back up on the server. Monthly the data are stored on an external device (USB hard disk) with a copy saved at head office in Mumbai. A backup server is available at the head office site, Dombivali, Mumbai. In addition, the procedure described retrieval of electronic data and restoring of backup.

The SOP on Good Chromatographic Practices described the procedure to be followed in HPLC/GC analysis. The procedure described sample sequence, the validity of system suitability, criteria for system suitability, use of bracketing standard, retention of invalid chromatograms with the report, use of autointegration, manual integration in the event of related substance test, reprocessing of chromatograms, printing of batch sequence and other details.

Out of specification and out of trend procedure was revised and discussed. The procedure described how OOSs are handled in a phased manner following the guidelines issued by the USFDA and MHRA. In 2018, a total of 8 OOS were reported, 2 valid and 6 invalid.

A separate SOP for trending and handling of out of trend results was in place which described the purpose and requirements of trending of critical quality system parameters and handling of out of trend results. From the procedure it was noted that alert and action limits are calculated using +/-3 and +/-4 standard deviation respectively. It was claimed that Statistical Process Control (SPC) and excel sheet are used for trend analysis. The logbook was maintained for OOT.

Incident and investigation related to QC laboratory were discussed. The procedure defined the term incident and differentiated against deviation. Basically, incidents were limited to unplanned laboratory events. The events were supported by various general and specific examples. The 2018 incidents were summarised and categorized into personal, chromatography and instrumentation. A total of 63 incidents were raised in 2018 whereas a total of 122 incidents were raised in 2017.

The stability program and the records of the batch Isoniazid were discussed. Samples were withdrawn based on stability study intimation slip, stability protocol and tested according to specification. A report on the previous 12 month test results was available. Stability samples were stored in various chambers.

Stability chambers in Plot M4.
- HM-07, accelerated humidity (40 ^{0}C, 75%)
- HM-06, intermediate humidity (30 ^{0}C, 65%)
- HM-05, real time humidity (25 ^{0}C, 60%)
- CC-01, cold chamber (2-8 ^{0}C)

Stability chambers in Plot N102.
- HM-03, long term stability (30 ^{0}C, 75%)
- HM-04, idle

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Validation

Process validation procedure, process validation protocol and report have been revised since the last WHO inspection containing a provision for annual verification of at least one batch per year.

The following processes in scope of the WHO inspection were verified:

- Lumefantrine
- Pyrazinamide

The hold time stability of DDFE1 was supported with a document titled: "Intermediate Analytical Report of Lumefantrine Phase III".

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections

12. Change control

The procedure was revised to address observations raised under the previous WHO inspection.

There were 102 changes recorded in year 2018 and none in 2019. The change on implementing a manufacturing process: reprocessing of lumefantrine batch tailings was discussed.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Rejection and re-use of materials

The SOP defined the basic principles of API reprocess and rework. The rejection of the input material and the release of the product was performed by senior manager QA. It was confirmed by the management of the Company, that manufacturing facility does not have any solvent recovery plant on site and no regenerated solvent is used. Only n-butanol is recovered which is used in the same stage (for Lumefantrine).

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Complaints and recalls

Handling of customer complaint was discussed. Complaints were categorized as critical, major and minor. The categorization was supported with examples and timeline established for the completion of complaints received from the domestic market (30 business days) and export market (6 months). In 2017, a total of 5 complaints were received related to Erythromycin (2 batches), Isoniazid (3 batches), Flucytosine (2 batches) and Erythromycin Oxime (4 batches). Most of these complaints related to brown particle and higher impurity level.

Handling of returned finished goods was discussed. There were two main reasons of returned goods, one due to business reason (commercial, tax issues, order cancellation) and another due to quality failures. Material returned due to commercial reason can be resale to other customer whereas materials returned due to quality failures shall be investigated. Register for the returned goods was maintained on a yearly basis.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Contract manufacturers (including laboratories)

Centre of Excellence located in Vapi, Valsad was qualified as an external laboratory. The qualification was based on a questionnaire and on-site assessment of the laboratory. The agreement was limited to particle size distribution by Malvern Size Analyser and other tests as needed. The laboratory was accredited to ISO 9001:2005 (July 2018) and ISO/IEC 17025:2005 (October 2017).

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

Part 3	Conclusion – Inspection outcome

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, ***Calyx Chemicals & Pharmaceuticals Ltd.*** located at ***Tarapur, Boisar. Dist. Palghar (Maharashtra), India*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

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 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 GMP for APIs or WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

2. 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 GMP*** or ***WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
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
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

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 HVAC Guidelines*** *or* ***WHO TRS No. 1010, Annex 8***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

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. 957, Annex 1
   http://www.who.int/medicines/publications/44threport/en/

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 2.
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

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

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

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

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***
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

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

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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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

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