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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Zhejiang Langhua Pharmaceutical Co.,Ltd.
Corporate address of manufacturer	21 Jiangxi St., Ningbo City, China Ninhua Group Co., Ltd
Inspected site	
Address of inspected manufacturing site if different from that given above	No. 7, Donghai 3rd Street, Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone, Linhai, Zhejiang China 317016
Unit / block / workshop number	Building 3/Workshop 034 Building 11/Workshops 110 and 113 Building 14/All Building 16/Workshop 161
Manufacturing license number	Zhe 20000303
Inspection details	
Dates of inspection	16 – 18 May 2016
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of APIs.
General information about the company and site	Zhejiang Langhua Pharmaceutical Co., Ltd. was formerly held by Sinochem Ningbo Ltd. and in 2015 the holding company changed its name to Ninhua Group Co., Ltd. The Ninhua Group has a diverse range of products including pharmaceuticals, agrochemicals and a HVAC business unit. Zhejiang Langhua Pharmaceutical Co., Ltd. was founded in 1986 as Xinhua Pharma Chemical Co., Ltd. Huangyan Zhejiang, was renamed as Zhejiang Xinhua Pharmaceutical Co., Ltd in 2005, and renamed as Zhejiang Langhua Pharmaceutical Co.,

	Ltd. in February 2013. The site is located in No. 7, Donghai 3rd Street, Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone, Linhai which is about a 45 minute drive from Taizhou city. The site is approximately 189278m^2 with buildings occupying approximately 35168 m^2. There are approximately 532 employees at the site. Zhejiang Langhua Pharmaceuticals manufactured 4 types of APIs at this site: Quinolone antibiotics (including Levofloxacin), Antivirus (Zidovudine), Cardiovascular and Antidepressant APIs. The APIs included the inspection scope were Zidovudine and Levofloxacin. Penicillin APIs and FPPs were no longer produced on the site. There were two previously used Penicillin production buildings: The production of penicillin FPP had been stopped in building 2 and the API production block building 4 had been dismantled.
History	This was the 3rd WHO GMP inspection, the last being in August 2013. The site is regularly inspected by the local CFDA and has also been inspected by ANVISA, EDQM and USFDA. It was stated that these inspections had a positive outcome.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients text: • Quality management • Personnel • Buildings and facilities • Process equipment • Documentation and records • Materials management • Production and in-process controls • Packaging and identification labelling of APIs and intermediates • Storage and distribution • Laboratory controls • Validation • Change control • Rejection and reuse of materials • Complaints and recalls • Contract manufacturers (including laboratories)

Restrictions	None
Out of scope	APIs not included in the scope of the inspection.
WHO product numbers covered by the inspection	Levofloxacin (APIMF 203) Zidovudine (APIMF167)

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

OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	**Brief summary of the findings and comments (where applicable)**

Brief summary of the findings and comments

1. Quality management

Principles

Responsibilities of the quality Unit(s)

The Quality Unit was divided into QA and QC with management responsibilities shown in an approved organization chart. Responsibilities were suitably described, including in position descriptions for key staff. The position descriptions reviewed were acceptable.

Responsibility for production activities

The structure and management responsibility for production activities was shown in an approved organization chart. Responsibilities were suitably described, including in position descriptions for key personnel. The position descriptions reviewed were acceptable.

Internal audits (self-inspection)

Not reviewed during this inspection.

Product quality review

Product quality review (PQR) was performed annually according to a SMP. Provided that processes were the same for different grades of API, all batches were included in the same PQR. The general approach was graphic display of results within 3σ, and Cpk where specified. The CAPA procedure was referred to if any action was needed.

The 2015 PQRs for Zidovudine and Levofloxacin APIs was reviewed and generally found satisfactory.

Both PQRs included reviews of critical process parameters, in-process controls, critical starting materials, recovered solvents, and QC test results, OOSs, deviations, changes, stability, returns, complaints and recalls. There had been no recorded returns, complaints or recalls during 2015.

2. Personnel

Personnel qualifications

There were a sufficient number of personnel who were suitably qualified through qualifications, experience and training. Responsibilities were well described, including in position descriptions for all personnel. Position descriptions for selected key staff were reviewed and generally found satisfactory.

Personnel hygiene

Personnel were required to wear protective clothing suitable for the type and stage of manufacturing. Suitable sanitation and change room facilities were provided. Smoking and eating was not permitted in manufacturing areas.

Although the details were not reviewed, it was understood that staff undergo an initial medical examination and this is periodically repeated.

3. Buildings and facilities

Design and construction

The buildings and facilities inspected were designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Manufacturing areas provided good space for the placement of equipment.

Utilities

Dedicated HVAC systems provided filtered air to cleanrooms used for final stages of processing to meet requirements for a Grade D environment. Specifications included pressure differentials between clean and non-clean area of at least 10Pa and at least 15 air changes per hour. The Grade D area was regularly monitored for airborne microorganisms and particulates (0,5 and 5.0µ) and also monitored using settle plates and contact plates.

Water

There were two purified water systems on site, installed in two different buildings.

The second PW system which supplied PW to workshops113 and 121 was installed in 2015. It's Phase I and II qualification had been completed. Phase III qualification was ongoing. The qualification documentation and test data were reviewed and discussed during the inspection.

Containment

Processing took place in closed systems wherever possible. The final synthesis, purification and packaging of Zidovudine took place in dedicated facilities to minimize the likelihood of cross-contamination. The final synthesis, purification and packaging of Levofloxacin took place in facilities shared with the

production of another API which was manufactured infrequently. Production was planned on a campaign basis and cleaning procedures had been validated.

Lighting

The lighting in all warehouses and production areas, and the QC laboratory was considered to be suitable.

Sanitation and maintenance

All areas inspected were clean and appeared to be well maintained.

4. Process equipment

Design and construction

Equipment used in the manufacture of Levofloxacin and Zidovudine APIs appeared to be of appropriate design and size for its intended use, cleaning and maintenance. Manufacture and material transfer took place in closed systems wherever possible.

Equipment maintenance and cleaning

Equipment was maintained according to a SMP which included requirements for preventive maintenance. For each API there was a maintenance plan for applicable equipment. Maintenance for a Levofloxacin dryer was reviewed and the specified requirements, frequency and records were satisfactory.

Equipment was required to be cleaned according to documented procedures and records maintained. The cleaning procedure and records for a centrifuge was reviewed as an example.

The operation procedure for a filter was also reviewed and the filter was required to be changed regularly. The replacement register was reviewed and considered acceptable.

Calibration

Calibration was performed in house according to documented procedures. Measuring equipment was required to be labelled with its calibration status and all examples viewed were within date.

Computerized systems

Computerized systems were not used for material or production control.
Computerized systems were used in the QC Laboratory.

5. Documentation and records

Documentation system and specifications

Activities were generally appropriately documented in SOPs. These were approved and version controlled. All records and other documentation requested during the inspection were readily available.

Equipment cleaning and use record

Equipment was required to be cleaned according to documented procedures for each type of equipment. Records were maintained and all equipment viewed appeared to be clean and suitably labelled with cleaning status.

Records of raw materials, intermediates, API labelling and packaging materials
Records of raw materials, intermediates, API labeling and packaging materials were maintained.

Master production instructions (master production and control records)
Approved master production instructions were available.

Batch production records (batch production and control records)
After copying master batch records, they were signed, dated and independently checked by a person in the quality assurance unit before use.

Laboratory control records
Laboratory control records, including a sample receiving and distribution register, and test records, were available for inspection.

Batch production record review
Two examples of completed BMRs were reviewed and found to be satisfactory.

6. Materials management General controls

Material suppliers were managed according to a SMP. Suppliers were classified as "normal" or "critical" (with some examples) and managed accordingly. The need for on-site audit was described in a matrix of material type and need for audit.

The supplier approval system was generally considered satisfactory and considered re-assessment, regulatory impact and changes to suppliers. An approved list of approved suppliers was available.

Receipt and quarantine
Materials were required to be checked on receipt, including for damage and verifying that the supplier was approved. They were placed in quarantine by cordoning off and labelling the storage location.

Bulk liquids were received from either dedicated tankers or tankers accompanied by a cleaning certificate. A sample from the tanker was taken before delivery through dedicated transfer hoses and the bulk tank placed in quarantine before re-testing.

Sampling and testing of incoming production materials
Production materials were sampled by QC in a designated sampling area and according to a defined sampling plan. The containers sampled were appropriately marked. After testing by QC, materials were released by applying a label to each container. The records viewed were satisfactory.

Storage
Materials were stored in designated areas of the warehouse, depending on the type of material. There was a separate locked area for reject materials.

Re-evaluation

Material release labels included a retest date.

7. Production and in-process controls Production operations

Production of Levofloxacin API took place in the different areas according to the manufacturing process.

The involved production areas were inspected and generally found to be of suitable standard, clean and logically organized to suit their intended purpose.

Where required, holding times were specified in the relevant BMR. As an example, the hold time study for a Levofloxacin intermediate, levofloxacin carboxylic acid was reviewed and found satisfactory.

In-process sampling and controls

In-process sampling and testing was performed at defined stages during processing. In-process samples were tested in the QC laboratory.

Blending batches of intermediates or APIs

Blending of Levofloxacin API batch tailings was permitted and performed according to a documented procedure and appeared to be satisfactorily controlled.

Blending validation protocol and report for Zidovudine were reviewed and considered acceptable.

Contamination control

Purification, drying and packaging stages of the production of Levofloxacin took place in non-dedicated facilities.

Production of Zidovudine took place in dedicated facilities.

Adequate precautions to minimize the likelihood of contamination, including final stages taking place in a Grade D controlled environment, were in place.

8. Packaging and identification labelling of APIs and intermediates

General

Packaging materials

Packaging materials were subjected to appropriate quality control testing before release. Non-compliances observed during the inspection that was listed in the full report regarding storage of printed API labels were addressed by the manufacturer to a satisfactory level.

Label issuance and control

Labels were issued according to a documented procedure and appeared to be adequately controlled.

Packaging and labelling operations

Packaging and labelling operations were appropriately described in batch packaging instructions. Line clearance was appropriately recorded.

9. Storage and distribution

Warehousing procedures

Finished APIs were stored in a designated warehouse and held in quarantine until released by the Authorized Person. A manual bin card system was used to control stock.

Distribution procedures

APIs and intermediates were released for distribution after they had been released by the Quality Unit.

10. Laboratory controls

General controls

The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments.

Testing of intermediates and APIs

QC testing was conducted as specified in the relevant specification and according to documented test methods. The sample receiving and distribution log book was checked and considered satisfactory.

Reference standards management procedure was reviewed. Secondary reference standards were prepared against the primary reference standards.

Validation of analytical procedures

HPLC equipment were used for assay and RS testing of raw materials, intermediate and APIs. HPLCs and GCs were networked by suitable systems. Access control and authorization of the functions of Lab Solution software and electronic data management procedures were spot checked during the inspection.

Stability monitoring of APIs

A range of stability chambers were available. Following initial stability studies to determine re-test date, at least one batch of API per year was required to be placed on on-going stability study.

Reserve/retention samples

There was a designated temperature controlled area for storage of retention samples. Retention samples were managed according to a SMP. Retention samples were stored under conditions of 15-25^{0}C and below 70% RH.

Handling of out of specification (OOS) results

A procedure for handling OOS was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding investigation of OOS were addressed by the manufacturer to a satisfactory level.

Microbiological testing

Microbiological testing took place in a separate and suitably equipped laboratory adjacent to the main QC laboratory.

Media was prepared in-house according to documented instructions with batch records maintained. Each prepared batch was required to be QC tested, including a growth promotion test. The records of media preparation reviewed were satisfactory.

Purified water testing and environmental monitoring (including particulates) of the Grade D cleanrooms was conducted according to documented procedures. These were reviewed during the inspection and plans and information on sampling locations. The results of water testing and environmental monitoring appeared to be satisfactory.

11. Validation

Validation policy

Validation policy for the whole site was described in a Validation Master Plan (VMP) which was updated annually. The VMP covered all aspects of validation including qualification, processes, test methods, utilities and cleaning. A validation committee with defined members had been formed to coordinate validation activities, with the Quality Director being ultimately responsible.

The VMP for 2016 was reviewed and appeared to be satisfactory.

Validation documentation

Validation protocols for Levofloxacin and Zidovudine APIs had been established to define how each validation would be conducted. Master manufacturing instructions were cross-referenced and critical process steps and acceptance criteria included. A validation report had been prepared for each API with results compared to acceptance criteria and a documented conclusion.

The process validation protocols and associated validation reports for Levofloxacin and Zidovudine APIs were reviewed and generally found satisfactory. Validation records for the manufacture of a batch of Levofloxacin API by blending released tailings was also reviewed and found satisfactory.

Qualification

Qualification of key equipment was a prerequisite for process validation and this was covered in the VMP. Qualification protocols and reports were available for key equipment. These were cross-referenced in the process validation documentation.

Approaches to process validation

Process validation was required to be either prospective or concurrent.

Process validation programme

The 2016 VMP included information on all validation activities conducted during 2015 and a plan for those due during 2016.

Periodic review of validated systems

The status of validated systems was reviewed annually during PQR. Processes were required to be revalidated every 3 years. Validation activities for Levofloxacin and Zidovudine had been conducted within this period.

Cleaning validation

The protocol and report for Levofloxacin cleaning validation were reviewed and generally found satisfactory. Carry over during the whole equipment chain was included as well as worst case sampling locations for each equipment. Diagrams of each equipment included sampling positions. Various methods for calculating maximum carry over were used, but ultimately 10ppm was used as worst case As some equipment was used to manufacture both Levofloxacin and another API, cleaning validation of this equipment was reviewed and found satisfactory.

Validation of analytical methods

Testing method validation was not reviewed during this inspection due to time constrains.

12. Change control

Change control

Change Control was managed according to a SMP. Several change controls CCs were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change control were addressed by the manufacturer to a satisfactory level.

Deviation

Deviation was managed according to a SMP and classified into minor, major or critical. Some deviations occurred in 2015 and 2016 were reviewed.

CAPA was managed according to a SMP.

The follow up CAPAs related to the above mentioned deviations were found satisfactory in general.

13. Rejection and re-use of materials

Rejection

Rejected APIs or materials were handled according to a SMP. They were required to be identified as such and held in the locked reject warehouse area. Rework was permitted by the procedure, but it was said to have never been done.

Reprocessing and Reworking

Reprocessing and reworking were done according to a SMP. Definitions were included with examples.

Reprocessing was required to be recorded in a supplement to the BMR and a log was maintained. Rework required a new BMR with a distinctive batch number. The change control procedure was used to determine and approve the rework procedure and the need for regulatory approval was considered.

Recovery of materials and solvents

Various solvents were recovered for use in the same step of manufacture only. Documented procedures were in place for solvent recovery. Records were maintained with batch number given and recovered solvent was tested by QC before release. Recovered solvents were stored in separate storage tanks.

The procedure and records for recovery of toluene were selected for review and generally found satisfactory.

Returns

Returns were required to be handled according to a documented procedure.

14. Complaints and recalls

Complaints were handled according to a SOP with responsibilities clearly defined and complaints classified by QA as either reasonable or unreasonable. All complaints were required to be recorded, including the reason for classification. Timelines for processing complaints were clearly specified and the need for immediate action (e.g. recall) considered.

Annual log books of complaints were required to be maintained. There were no recorded complaints for Zidovudine or Levofloxacin APIs.

There was a SOP described requirements for API recall. The composition of a recall team to handle any recall was described. Recalls were required to be classified into 3 levels according to risk with appropriate guidelines for each. There had been no recalls during 2015 and 2016. A mock recall was required to be performed annually and the record of this for 2015 was briefly reviewed.

15. Contract manufacturers (including laboratories)

There was no contract manufacturing of API or key starting materials. One analytical test for Zidovudine was contracted to an external testing lab.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned. Levofloxacin (APIMF 203) and Zidovudine (APIMF167) manufactured at Zhejiang Langhua Pharmaceutical Co.,Ltd.,located at No. 7, Donghai 3rd Street, Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone, Linhai, Zhejiang China 317016 were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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.
   http://www.who.int/medicines/publications/44threport/en/

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.
   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-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, 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
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.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
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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution 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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

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

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf