

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the API manufacturer**

Part 1	General information
Manufacturers Details	
Company information	
Name of manufacturer and address	Shijiazhuang Lonzeal Pharmaceuticals Co., Ltd. No. 16 West Ring Road, Shenze Shijiazhuang, 052560 China North latitude: N38°10'49.92" East longitude: E115°10'24.28" D-U-N-S: 528171743
Corporate address of manufacturer	As above
Inspected site	
Address of inspected manufacturing site if different from that given above	As above
Buildings and workshops	<ul style="list-style-type: none"> • Building No PF 05, Workshop 101 (dedicated - intermediates and final stages Lamivudine) • Building No PF 06, Workshop 302 (intermediates for Emtricitabin and for Lamivudine) • Building No PF 10, Workshop 104, ground floor (dedicated Workshop (WS) - Emtricitabin final stages) • Building No PF 10, Workshop 303 (dedicated WS - intermediates for Tenofovir Disoproxil Fumarate - PMPA) • Building No PF 01, Workshop 102 (Tenofovir Disoproxil Fumarate final stages, dedicated equipment) <p>Buildings and workshops listed above directly relate to production of APIs under the WHO PQ programme; the site has additional facilities for finished pharmaceutical products (outside the scope of this inspection).</p>
Manufacturing license number	No.: Hebei 20140001 issued by the national regional authority: Hebei Province Food and Drug Administration. Scope of Drug License: API (Lamivudine, Emtricitabine, Tenofovir Disoproxil Fumarate, Oxiracetam, Esomeprazole magnesium, Paroxetine Hydrochloride), Tablets, Granules, Capsules
Inspection details	

WHO public inspection report Shijiazhuang Lonzeal Pharmaceuticals, May 2017

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Dates of inspection	15 – 19 May 2017																											
Type of inspection	Routine, attention was paid to corrective actions and preventive actions (CAPA) implementation related to the previous WHO inspection – May 2016.																											
Introduction																												
Brief summary of the manufacturing activities	The manufacturer was involved in the manufacturing, packaging, labeling, testing and storage of the APIs and finished dosage forms.																											
General information about the company and site	<p>Shijiazhuang Lonzeal Pharmaceuticals Co., Ltd. was established in December 2006. It is a pharmaceutical enterprise which specializes in R&D, production and sales. Lonzeal's product line covers antiretroviral drugs (ARV) APIs and intermediates, supplying to pharmaceutical companies both domestic and international.</p> <p>The Company stated that around most part of their output production is Lamivudine.</p> <p>Manufacturing site is located at National Biopharmaceuticals Industrial Zone in Shenze, Hebei Province of China, accompanied with R&D center in Shijiazhuang City and commercial office in Beijing City.</p>																											
Brief report of inspection activities undertaken																												
Scope and limitations																												
Areas inspected	<ul style="list-style-type: none"> • Pharmaceutical Quality System • Documentation system • Production System • Facilities and Equipment System • Laboratory Control System 																											
Restrictions	N/A																											
WHO product numbers covered by the inspection	Emtricitabin (APIMF 221) Lamivudine (APIMF112) Tenofovir Disoproxil Fumarate -TDF (APIMF287)																											
Abbreviations	<table border="1"> <tr> <td>AHU</td> <td>air handling unit</td> </tr> <tr> <td>ALCOA</td> <td>attributable, legible, contemporaneous, original and accurate</td> </tr> <tr> <td>AQL</td> <td>Acceptance quality limit</td> </tr> <tr> <td>API</td> <td>active pharmaceutical ingredient</td> </tr> <tr> <td>APQR</td> <td>annual product quality review</td> </tr> <tr> <td>BDL</td> <td>below detection limit</td> </tr> <tr> <td>BMR</td> <td>batch manufacturing record</td> </tr> <tr> <td>BPR</td> <td>batch packaging record</td> </tr> <tr> <td>CAPA</td> <td>corrective actions and preventive actions</td> </tr> <tr> <td>CC</td> <td>change control</td> </tr> <tr> <td>CFU</td> <td>colony-forming unit</td> </tr> <tr> <td>CoA</td> <td>certificate of analysis</td> </tr> <tr> <td>CpK</td> <td>process capability index</td> </tr> </table>		AHU	air handling unit	ALCOA	attributable, legible, contemporaneous, original and accurate	AQL	Acceptance quality limit	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
AHU	air handling unit																											
ALCOA	attributable, legible, contemporaneous, original and accurate																											
AQL	Acceptance quality limit																											
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
FG	finished goods
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
ID	identity
IR	infrared spectrophotometer
IPC	In process control
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
NIR	near-infrared spectroscopy
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	preliminary hazard analysis
PM	preventive maintenance
PpK	process performance index
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
RH	relative humidity
RM	raw materials

WHO public inspection report Shijiazhuang Lonzeal Pharmaceuticals, May 2017

 This inspection report is the property of the WHO
 Contact: prequalinspection@who.int

RS	reference standard
SAP	system applications products for data processing
SFG	semi-finished goods
SOP	standard operating procedure
STP	standard test procedure
T	temperature
TAMC	total aerobic microbial count
TFC	total fungal count
TLC	thin layer chromatography
TMC	total microbial count
TOC	Total organic carbon
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
WFI	water for injection
WS	working standard

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

Brief summary of the findings and comments

1. Pharmaceutical quality system

In general the system for managing quality encompassed the organizational structure, procedures and processes. There were QA and QC departments that were independent of production. In general deviations from established procedures were documented and explained. Procedure was in place for notifying responsible management of regulatory inspections, serious GMP deficiencies, product defects and related actions.

The traceability of records and documentation system were satisfactory.

Product Quality Review (PQR)

The standard management procedure (SMP) “Product quality review” was discussed. The PQR covered but was not limited to:

- List of batches manufactured
- Yield and material balance for intermediates and finished product
- Summary of critical in-process controls
- Deviations, change controls, rejected materials
- Complaints
- Recalls, reprocessed and reworked batches
- Returned batches
- Environmental monitoring (EM) trend analysis in clean rooms
- Nitrogen system
- CAPAs related to the third party and regulatory audits

WHO public inspection report Shijiazhuang Lonzeal Pharmaceuticals, May 2017

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

- CAPAs related to the self-inspections (internal CAPAS)
- Stability and trends
- Vendors change summary
- OOS/OOT
- Intermediates
- Purified water (PW)
- Validation summary
- Contract analysis/tests
- Post-marketing commitments

PQR was performed annually and according to the SOP should be completed by the end of February of the following year.

Process capability was evaluated by statistical process control (SPC) by Cpk.

Process capability was calculated using Minitab software and practical application of Minitab was demonstrated during the inspection.

Quality risk management (QRM)

The SMP “Quality risk management” and register were discussed. Tools specified in the SOP were:

- Failure modes and effects analysis (FMEA) – used for premises, utilities, equipment
- Hazard analysis and critical control points (HACCP) – used for process risk assessment (RA).

The SOP “Failure modes and effects analysis” and SOP “Hazard analysis and critical control points” were discussed.

RA schedules were established for individual workshops. The SOP stated that quality risk review should be performed once per year during June – July. RA schedule for 2017 for workshop 101 was discussed.

RA No XX was discussed. The tool used for RA was FMEA.

RA No YY “RA report for manufacturing process of TDF” was discussed. The tool used for RA was HACCP.

Deviations

The SMP “Deviation management” and register were discussed. SOP was applicable to unplanned deviations. According to the SOP minor deviation should be closed within 5 days and major deviations should be closed within 15 working days. Deviation number and explanation of deviation was recorded in batch manufacturing / packaging records.

After the previous WHO inspection, the Company had put more emphasis in the SMP on root cause analysis (the deviation form itself was unchanged).

Deviations were classified as:

- Minor
- Major

Qualified person (QP) and Deviation Manager (a designated person from QA) were responsible for classification of deviations and final approval.

According to the SOP Ishikawa diagram, 5 Why`s and brain storming should be used for root cause analysis (RCA). It was noted that till the date of inspection only 5 Why`s were used.

Deviations were trended annually. Deviation No XX, classified as major was discussed.

The SMP “Deviation management in laboratory” and register were discussed. This SMP was applicable for deviations (incidents - obvious errors) that were not OOS/OOT. The procedure was a new one and no reviews or trend assessments had been performed yet.

Corrective actions and preventive actions (CAPA)

The SMP “Corrective and preventive actions”, flow chart and register were discussed. The SMP was applicable but not limited to:

- Deviations
- OOS/OOT
- Rejects
- Complaints
- Recall
- Self-inspection/external inspection
- Risk assented
- Returns
- Management review

According to the SMP, CAPAs were proposed by concerned departments, minor CAPAs were approved by a designated person from QA, major by QP; implementation was monitored by a designated person from QA.

CAPA No XX related to the deviation No YY was discussed.

Change control (CC)

The SMP “Change management”, change approval flow chart and register were discussed. CCs were classified by QA department as:

- Minor
- Major
- Critical

Changes were initiated by concerned departments. The SOP was applicable for GMP related activities.

CC No XX classified as critical was discussed.

CC No YY classified as major was discussed.

Management review (MR)

The SMP “Quality system management review” was discussed. Management review was comprised once per year. The SOP the following items should be covered by MR:

- Personnel
- Quality policy
- Quality plan
- Quality information communication
- Contract manufacturing an testing
- Vendors
- Technology transfer
- PQRs
- Effectiveness evaluation of Quality System
 - Deviations
 - CAPAs
 - CC
 - Interval/external audits
 - Quality risk management
 - Training
 - Complaints
 - Returns
 - Rejects
 - Reworking/reprocessing
- Suitability of quality standards
- Evaluation of data integrity
- Actions to be taken after last MR

Complaints

The SMP “Product quality complaints” and register were discussed. Complaint investigation XX was discussed.

Recalls

The SMP “Product recalls” was discussed. There were no product recalls in Company history. Recall effectiveness was evaluated by mock recall. According to the SOP a mock recall should be performed once in two years. Last class III mock recall was performed in April 2017. The Company mostly dispatched APIs directly to finished product manufacturers. In order to execute a recall, the Company traced paper-based “material cards” to find batches and dispatch dates, and subsequently retrieved respective shipment documents (maintained chronologically) for that time period to identify customers. Until the batch was still in the Company’s warehouse, the material card was stored in the warehouse. When the batch had been fully shipped, the card was archived.

Recalls were classified as following:

- Class I – should be initiated within 24 hours,
- Class II - should be initiated within 48 hours,
- Class III - should be initiated within 72 hours.

Self-inspection

The SMP “GMP self-inspection” was discussed. Items to be covered during self-inspections / internal audits included but were not limited to:

- Quality management
- Organization and personnel
- Premises and facilities
- Equipment
- Materials and products
- Qualification and validation
- Documents management
- Production
- QC and QA
- Contract manufacturing and testing
- Product release and recall
- Self-inspection
- CAPAs from previous self-inspection

Self-inspections were performed by teams, quarterly for selected departments and items, every 6 months complete self-inspection was performed. Internal audit schedule for 2017 was presented to the inspectors.

Self-inspection team members’ qualification files were available.

Audits were performed following a self-inspection protocol. Observations were recorded. CAPAs were submitted by the audited department and evaluated by QA. Follow-up was performed by QA.

Supplier qualification

The SMP “Material supplier quality assessment” was discussed. The SOP was applicable for all raw, packaging and auxiliary materials vendors. Suppliers were classified as:

- Class A – critical material vendors
- Class B – other than class A vendors.

Approved suppliers list was presented to the inspectors. Adding of new class A suppliers was performed via change control procedure. According to the SOP class A supplier audits should be performed every two years. Supplier audit schedule for 2016 & 2017 was presented to the inspectors.

Profile folders were maintained for each supplier; annual supplier-specific quality reviews were conducted.

Personnel

The current organization chart of the company was available. The company had sufficient number of personnel with responsibilities according to their respective unit and department.

According to the company presentation, the site employed approximately 436 full time employees, among which 211 were involved in production, 42 were in QA and QC.

Personnel were wearing clothing suitable for the manufacturing activities.

The SMP “Employees training” was discussed. Attention was paid to analyst training and qualification.

2. Documentation system

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures.

Production, control and distribution records were retained for one year after the expiry date of the batch. For APIs with retest dates, records were retained for three years after the batch was completely distributed. Specifications were established for raw materials, intermediates and APIs. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories. The Company had a policy to archive all logbooks (equipment usage, maintenance etc.) of the previous year.

3. Production system

In general production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Deviations from procedures were recorded; major deviations were investigated. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use. The processing status of major units of equipment was indicated.

Manufacturing operations of the PMPA (intermediate for TDF) in workshop 101 were stopped in May 2016 (after the previous WHO inspection). During the previous WHO inspection the dedicated workshop 303 for manufacture of PMPA was under construction. WS 303 utilities and equipment were installed in an existing building. IQ and OQ of the equipment was performed in July 2016, PQ was performed together with the PMPA manufacturing process validation in February 2017. WS 303 reconstruction was done by change control procedure. Technology transfer protocol XX and report YY and GAP analysis ZZ were discussed.

The set of critical process parameters had been enlarged for PMPA, partly resulting from the respective RA, partly because the new 303 was larger than the previously used production unit for PMPA.

PMPA validation protocol XX and report YY were discussed.

A number of batch manufacturing records BMRs were discussed.

TDF validation protocol XX and report YY were discussed.

With regards to mother liquor recovery, the Company stated that relevant specifications were established for Lamivudine and Emtricitabin processes; recovery had been practiced for Lamivudine.

With regards to solvent recovery, the Company stated that for TDF final stages only fresh solvents were / will be used, as TDF output was small.

WS 101 (Lamivudine) had a solvent recovery area next to it, identified as building PF07. WS 104 (Emtricitabin final stages) had a solvent recovery area next to it, identified as building PF11 (open, under cover). Solvent recovery was not inspected.

4. Facilities and equipment system

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups and contamination. Generally the permanently installed pipework was appropriately identified.

Newly reconstructed WS 303 for production of PMPA was inspected. This was not covered by the previous WHO inspection. The Company was planning to submit variation to the dossier APIMF287 regarding the WS 303. PMPA production was performed on three floors. WS 303 was said to be PMPA dedicated WS. All reactors, other equipment and connecting pipelines in WS 303 were newly installed.

IQ/OQ/PQ protocols and reports of the reactor No XX and dryer YY were discussed. The SOPs for maintenance of the dryer and enamel reactor and preventive maintenance schedule for WS 303 for 2017 were discussed.

T sensor XX calibration was checked. The Company explained that several calibrations were done on-site in the building PF04 (not visited during the inspection).

Measuring devices calibration schedule for 2017 was presented to the inspectors; the schedule was established for the whole site.

Maintenance schedules were established by workshops; the schedule also included equipment specific check-lists.

Utilities

Purified water system (PW) for WS 104 was inspected. Bore well was used to get source water. PW was produced by two stage reverse osmosis (RO). PW system was installed in March 2015. PW was used for cleaning equipment, tools and clean rooms and for washing garments used in clean rooms. PW was in continuous circulation at ambient temperature (T). Conductivity and flow rate were checked on line. PW storage tank and loop were sanitized once per month using hot water at 80 – 85 °C for 2 hours. PW storage tank and loop were made from stainless steel 316 L. PW system was well maintained.

PW microbiology trends for 3rd phase validation June 2015 – July 2016 for WS 104 were discussed. Trends were presented as 3 sigma.

Air handling unit AHU I, supplying air to workshop 102 was inspected. Re-circulated air was used in clean rooms. Primary filter was G4, secondary F8. Terminal HEPA filters H13 were installed in the rooms. G4 and F8 filters were changed regularly, depending on pressure differentials or time period, whichever occurred first. Pressure differentials between G4 and F8 were continuously monitored by software. HEPA filters integrity tests were contracted out and performed annually, according to the national standard. AHU was well maintained.

The SOP “SOP for WS 102 air conditioning system” was discussed. Maintenance of AHU was the responsibility of engineering department, maintenance of filters was the responsibility of production department.

Nitrogen was produced on-site and stored in the compressed gas form. The Company stated that WS 101 and 102 had a common N2 system, WS 104 had its own system. Nitrogen production was not followed up during this inspection.

Environmental monitoring (EM)

EM trends for 2016 for WS 101 clean rooms were discussed. Action and alert limits were set up. Settle plates (purchased ready-made) were exposed for 4 hours, validation protocol/report XX were discussed.

5. Laboratory control system

Laboratory areas were separated from production areas.

Finished API release testing, finished API stability testing, hold-time testing for intermediates were performed in the “Analytical center”, located in the administrative building.

In process control (IPC) was performed in workshops. Structurally IPC was under the QC department. The Company stated that IPC labs operated 24 h if necessary.

IPC laboratory located at PMPA WS 303 was inspected. The laboratory was also used to test IPC samples from WS 101 (Lamivudine), when IPC capacity in 101 was not sufficient. 3 HPLCs were installed for IPC tests; all connected to the Chromeleon 7.2 software. Usage logbooks of a number of HPLCs were checked.

The SMP0 “Processing out of specification (OOS) and out of trends (OOT) results”, its flow chart and register were discussed. The procedure was applicable to tests performed in the “Analytical center” (intermediates / solid products, finished APIs – products for which a quality specification had been approved) and Microbiology laboratory.

Reference standards were stored under controlled conditions. The current working standard of Lamivudine had relevant documentation available.

The SMP “Access permission of chromatogram workstation” and access level log book were discussed.

The SMP “Manual integration (MI)” was discussed. According to the SMP the analyst should fulfill an MI request form prior to performing MI; the form should be approved by QC department manager. The Company stated that MI procedure was not applicable to IPC tests.

The SMP “Finished product release” was discussed. APIs were released by QP, who was also the QA manager.

The SMP “Electronic data management”, backup and data retrieval registers/logbooks were discussed.

Excel sheets were used for assay and impurities calculations. Excel validation protocol/report XX were discussed.

The SOP “Use of culture media” and R2A media preparation log book were discussed.

API reserve samples were retained for one year after the expiry date and stored in the same packaging system in which the API was stored. Reserve samples for APIs with retest dates were retained for three years after the batch was completely distributed.

Stability studies for PMPA produced in the newly reconstructed workshop 303 were initiated in March, for finished TDF in April. By the time of the inspection, accelerated stability study results for PMPA (1M) were finished. PMPA stability protocol No XX and 1M analytical test data were discussed.

Electronic raw data of chromatography testing generated with the old software (not with the server based Chromeleon 7.2) was retained on a single set of CDs.

PART 3 CONCLUSION

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, as well as corrective actions taken:

- Emtricitabin (APIMF 221)
- Lamivudine (APIMF112)
- Tenofovir Disoproxil Fumarate (APIMF287)

manufactured at Lonzeal Pharmaceuticals Co. (workshops No 101, 102, 104, 302 and 303), located at No. 16 West Ring Road, Shenze Shijiazhuang, 052560 China (People's Republic of), was considered to be manufactured in compliance with applicable sections of 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 used for assessing compliance

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
Short name: WHO TRS No. 957, Annex 2
<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/
Short name: WHO TRS No. 986, Annex 2
3. 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

4. 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
Short name: WHO TRS No. 970, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
5. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1
6. 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
Short name: WHO TRS No. 961, Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
7. 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
8. WHO Good Practices for Pharmaceutical 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/>
9. 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/>
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
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
Short name: WHO TRS 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
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
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
Short name: WHO TRS 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
Short name: WHO TRS 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
Short name: WHO TRS 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
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf