World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

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

Part 1	General information
Manufacturers details	
Company information	
Name of manufacturer	Shenyang Antibiotic Manufacturer
Corporate address of manufacturer	Shenyang Tonglian Group Co. Ltd. No.18 Yucai Lane, East Shuncheng Road, Dadong District, Shenyang, P.R. China
Inspected site	
Address of inspected manufacturing site if different from that given above	Jianshebei, North Third Road, Hushitai Town, Xinchengzi District, Shenyang, Liaoning, China, 110122. Latitude: 41°57'1.58"N Longitude: 123°30'57.66"E
Unit / block / workshop number	Workshop 103
Manufacturing license number	20150030 issued by Liaoning FDA
Inspection details	
Dates of inspection	30 July - 02 August 2018
Type of inspection	Routine re-inspection
Introduction	
Brief summary of the manufacturing activities	Shenyang Antibiotic Manufacturer has two workshops for the manufacturing of APIs. Workshop 103 was dedicated to the manufacture of Rifampicin Polymorph-II and Rifampicin Polymorph-I. The facility and equipment were shared by the two polymorphs up to the stage of producing the crude Rifampicin. The final manufacturing stages of the API were performed in separate facilities. Polymorph-I and Polymorph-II manufacturing activities were carried out in separate areas in the Grade D clean area. Workshop 201 was used for manufacture of another API.
General information about the company and site	Shenyang Antibiotic Manufacturer, founded in 1992, is owned by the Tonglian group, with the group having many operational units at various locations across China, such as Shanghai and Inner Mongolia and produce intermediates and APIs, with the main API being Rifampicin. The factory was surrounded by residential buildings and other

	factories, the total number of employees was approximately 604 at the time of inspection. No highly sensitizing materials, high potency or toxicity materials were produce on the site.
History	This was the fourth inspection conducted by WHO. The Rifampicin API was pre-qualified in 2016. The last inspection of this site was conducted from 20-22 July 2015. No foreign agency had previously inspected the site for Rifampicin API.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	<u>Documents review included</u> • 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 <u>Areas visited:</u> Workshop 103 for Rifampicin Polymorph-II API manufacturing, QC laboratories including chemical and microbiology, Warehouse, Purified water plant, HVAC
Restrictions	N/A
Out of scope	Other APIs and workshops outside of the inspection scope were not visited.
WHO product numbers covered by the inspection	Rifampicin API (APIMF083)

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

A formal documented system for quality assurance was established, with procedures covering key quality elements being in place. Operations were specified in written form and critical GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Managerial responsibilities were in general appropriately specified in written job-descriptions. Product and processes were monitored and the results considered during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures. The Quality Department was divided into QA and QC, which was separate from the production department.

Product quality review

Annual product quality review was performed according to an SOP. All batches manufactured during January to December were required to be reviewed. Annual PQR were required to be complete before end of March of the following year. The 2015, 2016 and 2017 PQRs for Rifampicin Polymorph II were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding PQR were addressed by the manufacturer to a satisfactory level.

Quality Risk Management

Examples of risk analyses were reviewed in the change control documents. Non-compliances observed during the inspection that was listed in the full report regarding risk management were addressed by the manufacturer to a satisfactory level.

Internal audits (self-inspection)
Self-inspection was conducted according to an SOP which was elaborate and detailed. Unscheduled self-inspection was catered for in the procedure. The self-audit plan for 2018 provided information on the auditee department, self-inspection team, scheduled month for the audit and closure of audits. Documents identified a list of auditees to be used for self-inspection provided for designee in the team with qualification and experience and a communique to the concerned department of a planned self-inspection.

Self-inspections reports conducted of the QA department and the production department in 2018 were reviewed. Audit findings were documented and corrective actions taken.

Deviations
Deviation was managed according an SOP. Deviation logbooks for 2017 and 2018 were maintained. An example of critical deviation and CAPA regarding the testing of Rifamycin S-Na were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding quality testing were addressed by the manufacturer to a satisfactory level.

CAPAs
CAPAs were managed according to an SOP. CAPA template was attached to the SOP including corrective, preventive and effectiveness evaluation. CAPA logbooks for 2017 and 2018 were available and checked. CAPAs to the major deficiencies raised in the last inspection were checked and found generally acceptable.

2. Personnel

Personnel qualifications
There appeared to be an adequate number of personnel to perform and supervise the manufacture of Rifampicin API. Key personnel had adequate qualifications and experience. Responsibilities were described in job descriptions. The key personnel had some changes since the last inspection, including QA Head, QC Head, Production Head and Equipment Head.

Personnel hygiene
Personnel were required to wear protective clothing appropriate to the stage of production and quality control requirements.

Training
A personnel training management procedure was briefly reviewed and discussed. Induction, on-the-job and current GMP training were all included. Annual training plans were reviewed for relevant staff within WS103. Training files were reviewed for the newly appointed Production Head and the analyst involved in potency testing of Rifamycin S-Na. All training received was duly recorded. Retraining is performed in a specified time interval.

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 and clean space for the placement of equipment.

The company clarified the status of buildings indicated on the site lay out in the SMF. Workshop 103 was dedicated to Rifampicin API production including chemical area for synthetic process and Grade D clean area for final purification, drying and packaging. The design and construction of this workshop was considered acceptable. A suitable area for in-process testing had been provided within the production block. The main QC laboratory was located in a separate building.

Water system
Purified water was not used in the final stage of Rifamycin API production. The purified water system was briefly visited. PW was supplied to the area via stainless steel pipes. The direction of water flow was indicated and samplings points were provided.

Air handling units
HVAC units were in place that provided filtered clean air to Grade D production areas in WS103. Pressures differential and temperature in Grade D production area was monitored. Air from rooms where open product was handled was not recirculated. The air was passed through a dust collector which was managed according to an SOP.

Lighting
Lighting in the areas visited appeared to be appropriate.

Containment
Rifampicin was produced in workshop 103 which was dedicated to the production of this API.

Sanitation and maintenance
The Rifampicin production blocks was clean, tidy and appeared to be suitably maintained.

4. Process equipment

Design and construction
Equipment used for the production of Rifampicin API appeared to be of appropriate design and size for its intended use. Major equipment and processing lines were appropriately identified. The equipment used for manufacturing Rifampicin was dedicated to this API.

Equipment maintenance and cleaning
Equipment maintenance procedure was in place. Documented cleaning procedures were available for equipment.

An SOP for equipment cleaning procedure was reviewed and acceptable. This SOP related to the cleaning of acidification reactor, cyclization reactor, concentration reactor and the connecting lines.

Labeling of equipment
Generally all equipment was clearly identified with a unique number. Their status was apparent from unambiguous labels attached.

Calibration of equipment
The calibration of the standard temperature digital display was spot checked. The acceptance criteria and testing record was available.

Computerized systems
Computerized systems were used in the QC lab, but not in the production of Rifampicin API.

5. Documentation and records

Documentation system
An SOP addressing documents management system was in place. The responsibilities, distribution and control of documents were found acceptable. The retention time for different types of documents was verified and it was observed that documents and records were retained according to the in house procedure and requirement. The archival and retrieval of documents was well organized.

Batch numbering system
Material code was used in the different stage of the production. A new numbering system for dried material was introduced as per an SOP in 2018. Traceability has been improved by the use of the system.

Batch production records (batch production and control records)
The approved master formula of Rifampicin was checked and compared to the operational formula. BMRs for several batches were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding BMRs were addressed by the manufacturer to a satisfactory level.

6. Materials management

Supplier qualification
The supplier audit management system was briefly discussed. This SOP required an on spot audit to be performed for key starting material and primary packaging material suppliers.

The 2017 and 2018 annual suppliers audit plans were reviewed. Realization dates were added to the plan after an audit. The supplier of the inner plastic bags was audited on site. The report of audit was reviewed. The documentation of audits and further justification for supplier qualification appeared acceptable.

Quality agreements
As an example of a quality agreement the contract with the supplier of a solvent was reviewed. All GMP requirements were addressed.

Tank farm

Solvents were kept in large tanks in an open, dedicated part of the warehouse. Tank solvent management procedures described the details for sampling and operation. Non-compliances observed during the inspection that was listed in the full report regarding solvent sampling and fixed transfer pipe labelling were addressed by the manufacturer to a satisfactory level.

7. Production and in-process controls

Rifampicin was produced in two polymorphs. Two product codes were applied, 80 for Polymorph I and 81 for Polymorph II. The Rifampicin Polymorph II could be released according to one of 6 specifications: BP, EP, USP, IP, CP and WHO. Blending was part of the process.

The chemical area of 103 workshop was briefly visited. The area looked clean and well maintained generally. The manufacturing process was checked together with equipment. All equipment was labelled with respect to their status. Balances of various sizes were all calibrated and provided at their place of need. All the pipes and tubes in the area were provided with labels and direction of flow. Labelled trolleys were provided at the crude product centrifugal room to transport product.

A tour was made of the Grade D rooms where Polymorph II type Rifampicin was purified. Room pressures were indicated with pressure gauges. Gowning looked to be adequate for Grade D areas in general. The SOP on washing of operators clothes was briefly reviewed. Clothes for the area for Polymorph II material were washed separately from clothes worn in the Polymorph I area.

Logbooks were checked for the use of sifter and mill as well as their cleaning. Cleaning SOP was briefly reviewed and was acceptable.

Contamination control

All operations following the chemical stage were carried out in a Class D environment. The environmental monitoring review for 2015 was verified indicating that the rooms were well control.

8. Packaging and identification labelling of APIs and intermediates

The area for packaging of the final API was visited. During the visit no operations were ongoing.

9. Storage and distribution

Warehousing procedures

A visit was made to the warehouses. The area was generally spacious and well lit. Designated storage areas for different types of starting materials and finished API were available. Segregated areas for the storage of quarantined, rejected, returned and recalled materials were in place. Receiving bays were protecting the products from adverse weather conditions.

A list of qualified manufacturers and suppliers was used. A sampling room was present where QC staff would sample of starting materials. The first-in-first-out principle was applied. Temperature sensors were placed at worst case locations determined by a mapping study. In some areas A/C devices were placed to keep the temperature within range.

The procedure was discussed for the cleaning of drums used to transport solvents to Workshop 103. No comment was made.

Final product Rifampicin Polymorph II was stored in a dedicated warehouse. Reject and quarantine cages were available. From the inventory sheet with a batch it was seen that repackaging operations took place. These operations would be done in the packaging area in WS 103.

Distribution procedures

Rifampicin API was distributed following release by the Quality Assurance department. Storage conditions, including during transport, were specified on the API label. The product release management procedure was checked. Non-compliances observed during the inspection that was listed in the full report regarding product release were addressed by the manufacturer to a satisfactory level.

10. Laboratory controls

General controls

The QC chemical laboratory and microbiological laboratory were visited during the inspection. The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments.

Sample receiving and distribution

Sampling procedure, sample receiving and distribution logbook were checked in the chemical QC laboratory.

Sampling activity was inspected. Non-compliances observed during the inspection that was listed in the full report regarding sample management were addressed by the manufacturer to a satisfactory level.

Testing of intermediates and APIs

QC testing was conducted as specified in the relevant specification and according to documented test methods. Test parameters for WHO grade Rifampicin API were listed in a documented specification. The computer access control, authorization of the functions and testing data were checked during the inspection. Non-compliances observed during the inspection that was listed in the full report regarding computerized systems validation were addressed by the manufacturer to a satisfactory level.

OOS management

An OOS handling procedure was reviewed. The scope of OOS and investigation flow chart was discussed. 2018 OOS logbook, an OOS investigation file and records was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding OOS management were addressed by the manufacturer to a satisfactory level.

Reserve/retention samples

Retention samples were kept in an air-conditioned room maintained at ≤20ºC and RH 40-65%. Records of daily checks of these conditions were satisfactory.

Samples of Rifampicin API Polymorph I and II were stored in separate designated areas within the room. Samples were stored in small bags of the same material as for commercial batches and these were stored in closed fiber drums with a good indexation system.

Stability monitoring of APIs

A range of stability chambers were available. Stability monitoring program and samples were available and checked. A logbook of the samples in-warded and withdrawn was available and acceptable.

Data management

The company currently is operating only partially networked HPLC and GC equipment. Basic data integrity controls were in place.

Microbiological testing laboratory

A tour was made of the microbiological laboratory. The area was generally suitable for its activities. At the main entrance to the laboratory location, mouse traps were in place. Gowning procedure was in place.

Access to the media preparation area required hand washing and secondary gowning, the procedures to this were provided in an SOP and pictorial depiction provided. Purified water testing records for microbial limits was reviewed. The sampling points were appropriately identified. Testing was done according to an SOP. Trending reports of PW was available in the Rifampicin WHO grade PQR 2017.

Microbial limit testing for Rifampicin API was performed according to BP method. No comments were made.

The Micro Lab OOS procedure was briefly reviewed. No comments were made on this procedure.

11. Validation

Validation Master Plan

A Validation Master Plan was made yearly as required by an SOP. In addition there was an SOP on validation management procedure. A validation matrix listing the current validated state of processes and equipment and an annual validation schedule per department were documented.

Qualification

Equipment qualification procedure was in place and the practice was found acceptable. The following documents were reviewed and acceptable:

- Equipment requalification SOP
- Validation management procedure SOP. A complete equipment qualification list was in place.
- Crystallization tank requalification
- Re-qualification documentation for AHU

Process validation

A CAPA was discussed which was in response to an observation regarding process validation from the 2015 inspection. A process validation exercise was set up. The PV report was reviewed. The study was well designed and the report was conclusive.

A process re-validation report was reviewed. The frequency of re-validation was once every three years unless there was a major change in a process or facility. There were no deviations and change controls reported during manufacturing of all batches.

Analytical method validation

Analytical method revalidation protocol was presented and reviewed. Before validation risk analysis was performed and equipment was verified for its calibration and qualification status before demonstration of analytical procedure for its intended use. Non-compliances observed during the inspection that was listed in the full report regarding the method re-validation were addressed by the manufacturer to a satisfactory level.

Cleaning validation

Cleaning validation had been performed and was documented.

PW system validation

This had been performed for Workshop 103 during 2016-2017.The study was found acceptable. PW was not used in the final purification but used in the earlier stage of processing and in equipment cleaning.

Computerized system (CS) validation

SOP for CS validation was reviewed. Computerized system validation for HPLC system was spot checked. The system networked HPLCs including Waters and Shimadzu. Non-compliances observed during the inspection that was listed in the full report regarding the CS validation were addressed by the manufacturer to a satisfactory level.

12. Change control

The SOP for change control was reviewed. Types of changes were minor, moderate or major. A trend analysis and review of changes was made every year and the report for 2017 was discussed. A number of change control records were reviewed.

13. Rejection and re-use of materials

Rejection

Several SOPs relevant to handling material rejection were available for inspection. No comments were made.

Reprocessing

Reprocessing management procedure was in place. Reprocessing required QA approval. A Reprocessing log book was kept.

Reworking

Reworking was not permitted.

Recovery of materials and solvents

Recovery of solvents took place in a designated area using separate equipment for each solvent according to SOP .Recovered solvents were tested according to the specification and released by QC. Recovered solvents could only be used for the same process as the original solvent was used and only for the same polymorphic form of API.

Returns
Returned API was required to be placed in a designated area within the warehouse. It was stated that there had never been any returned Rifampicin API.

14. Complaints and recalls

Complaints
An SOP for customer complaint management was in place. There was no customer complaint reported in the last three years for Rifampicin API (Polymorph-II) for WHO grade.

Recall
There was no product recall in the last three years. As per SOP, recalls were of two types, voluntary recall and mandatory recall. Further these recalls were classified. A mock recall was performed on in 2018 to mimic a class I recall.

15. Contract manufacturers (including laboratories)

The intermediate Rifamycin S-Na was manufactured by the sister company Hulunbuir North Pharmaceutical Co. Ltd. QC testing of Rifampicin API for polymorphic form was contracted to a university laboratory.

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, Rifampicin API (APIMF083) manufactured at ***Shenyang Antibiotic Manufacturer*** located at ***Jianshebei, North Third Road, Hushitai Town, Xinchengzi District, Shenyang, Liaoning, China*** was 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-eighth 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-sixth 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.* Fiftieth 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*. Fiftieth 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.* Fiftieth 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.* Fiftieth 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