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	Zhejiang Jiangbei Pharmaceutical Co., Ltd.
Corporate address of manufacturer	Dongdai Zhang'an Street, Jiaojiang District, Taizhou City, 318017, Zhejiang Province, *The People's Republic of China*
Inspected site	
Address of inspected manufacturing site if different from that given above	Same as above
Unit / block / workshop number	Workshops 02 Building 11(A) Workshop 06 Buildings 09, 23,25.
Manufacturing license number	Zhe 20060462
Inspection details	
Dates of inspection	10 to 13 May 2016
Type of inspection	Initial inspection (New site)
Introduction	
Brief summary of the manufacturing activities	Production and quality control of APIs.
General information about the company and site	Zhejiang Jiangbei Pharmaceutical Co., Ltd. is a privately owned company founded in 1993 as Jiangbei Chemical Factory. In 2004 it became Zhejiang Jiangbei pharmaceutical Co., Ltd. There were approximately 370 employees in total at the time of inspection, 72 in the Quality Unit and 174 in production departments. The main APIs produced at the site were anti-hyperlipidemics, anti– epileptic and anti-virals. Starting material and intermediate used in the manufacture of Efavirenz were also produced at the site. There were no toxic or hazardous substances such as antibiotics, hormones or cytostatics manufactured at this site.

	The company had recently completed a new workshop for the manufacture of finished pharmaceutical products.
History	*This was the first WHO inspection. The site had also been inspected by the USFDA, KFDA, German Health Authority and EDQM for a different API.*
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	No
Out of scope	No
WHO product numbers covered by the inspection	• Efavirenz (APIMF283) • Intermediate (S)-5-chloro-_-(cyclopropylethynyl)-2-amino-α-(trifluoromethyl)benzyl methanol (EV-1) for Efavirenz (APIMF253)

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 and was the responsibility of the Quality Director. Responsibilities were well described, including in position descriptions for key staff. The position descriptions reviewed were detailed.

Responsibility for production activities

The Production Director had overall responsibility for managing production activities and there was a manager for each of the production workshops. Responsibilities were well described, including in position descriptions for key personnel. The position descriptions reviewed were detailed.

Internal audits (self-inspection)

Internal audits were performed according to a SOP. Each department was required to be audited annually, but there was provision for this to be more frequent if necessary. QA had overall responsibility for the programme and it was specified that auditors could not inspect their own department.

Deficiencies noted during internal audits were classified as "critical", "major" or "minor" with appropriate definitions for each. Deficiencies noted were handled by the CAPA system.

An annual internal audit plan was required to be prepared by QA and approved by the Quality Director. The plan for 2016 was reviewed and appeared satisfactory. Detailed internal audit reports were not reviewed.

Product quality review

PQR was performed according to a SOP with the stated objective of demonstrating the stability, reproducibility and reliability of processes and products. It was required to be done annually using data from all batches of APIs. The SOP specified the review of IPC test results and API test results, summary of validation work done, OOS batches, deviations, changes, stability monitoring, returns, complaints and recalls, and adequacy of CAPAs.

The 2015 PQR for Efavirenz API and intermediate E05 manufactured were reviewed. The methods used to analyse data, the conclusion and final approval of these PQRs generally appeared to be satisfactory. 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

There was a procedure for Quality Risk Management in place. Various approaches to risk assessment were allowed. The risk reports related to the workshop and product in the inspection

scope were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding quality risk management were addressed by the manufacturer to a satisfactory level.

Deviations

The procedure for handling deviations was reviewed. There were three types of deviation mentioned in the procedure.

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. The position descriptions reviewed were detailed.

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.

The final synthesis, drying and packaging of Efavirenz API were performed in a dedicated facility. Final crystallization took place in a controlled but not classified area and centrifuging, drying and packaging in a Grade D clean area.

Utilities

A dedicated HVAC system provided filtered air to the area used for final synthesis, drying and packaging of Efavirenz API to meet requirements for a Grade D environment. Specifications included pressure differentials between clean and non-clean area. The Grade D area was regularly monitored for airborne microorganisms and particulates and also monitored using settle plates and contact plates.

Water

Purified water used in the final stages of Efavirenz API manufacture was produced by a water system located in the same workshop. The system was a modern design using double reverse osmosis and EDI to produce purified water meeting EP, USP and CP specifications. Purified water was distributed by a 316SS loop. The water system appeared to be well maintained and the results of regular monitoring indicated that it was under good control.

Containment

The final synthesis, purification and packaging of Efavirenz took place in a dedicated facility to minimize the likelihood of cross-contamination. In areas where dust might be produced (e.g. milling), the area was maintained at negative pressure to adjacent areas.

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 Efavirenz 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
All equipment viewed appeared to be clean and well maintained.

Equipment was required to be cleaned according to documented procedures. Records were maintained and equipment status was indicated by sign on each of equipment.

Equipment preventive maintenance was performed according to a SOP and records maintained. A maintenance plan was available. As an example, the procedure and records for the maintenance of glass lined reactors was reviewed and found 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.
Computer system was used in QC lab for HPLC and GC networking.

5. Documentation and records

Documentation system and specifications
Documents were managed according to a SOP. Activities were documented in SOPs and other appropriate documents such as batch manufacturing records (BMRs). These were approved and version controlled. All records and other documentation requested during the inspection were readily available. Non-compliances observed during the inspection that was listed in the full report regarding production records were addressed by the manufacturer to a satisfactory level.

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. A non-compliance regarding a cleaning procedure was satisfactorily corrected.

Records of raw materials, intermediates, API labelling and packaging materials
Suitable records of raw materials, intermediates, API labelling 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 testing records were kept and available in general.

Batch production record review
The productions records for a batch of Efavirenz released in 2016 and the associated records for the intermediates used in this batch were reviewed. These records appeared to have been properly completed and reviewed.

6. Materials management

General controls
Procedures for the receipt, quarantine, storage, handling, sampling, testing and approval or rejection of materials were inspected and generally found satisfactory.

Receipt and quarantine
On receipt, materials were checked for damage and against the approved supplier list. They were labelled segregated and quarantined by cordoning using yellow rope.

Sampling and testing of incoming production materials
Materials were sampled by QC following a documented sampling procedure and tested by QC before release. The containers sampled were labelled with a suitable label.

Storage
Materials were stored in designated warehouses that were generally well organized, clean and tidy. Where storage conditions were not specified, temperature and humidity was monitored and records maintained. However, the relevant SOP specified action to be taken if these were exceeded under certain conditions.

Efavirenz API was stored in a warehouse provided with environmental control. Records indicated that the specified conditions had been maintained.

Re-evaluation

The approved label applied after release included a retest date. All materials examined were within this date.

7. Production and in-process controls

Production operations

Production of Efavirenz took place in different workshops. All of the production areas for Efavirenz were inspected and generally found to be of suitable standard, clean and logically organized to suit their intended purpose.

In-process sampling and controls

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

Blending batches of intermediates or APIs

Blending of API batch tailings was permitted with the expiry of the shortest expiring batch allocated to the blended batch. Blending was performed according to a documented procedure and appeared to be satisfactorily controlled.

Contamination control

API synthesis, purification, crystallization, drying and packaging was performed in facilities dedicated to Efavirenz.

8. Packaging and identification labelling of APIs and intermediates

General

Packaging materials

Packaging materials were appropriately stored and subjected to quality control testing before release.

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

There were documented procedures for the receipt, quarantine, sampling and release of materials. Computerized systems were not used for material control and a manual bin-card system was used. The materials reviewed had been controlled according to the procedures and no issues were noted.

Distribution procedures

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

10. Laboratory controls

General controls

There were two QC labs on the site, one for API and one for FPP. The company had an organized and suitably equipped QC laboratory for API testing.

Testing of intermediates and APIs

The sample receiving and distribution log book was checked. Samples for testing were kept in a designated area.

Secondary reference standards were prepared against the primary reference standards, the usage log was checked. The shelf life of working reference of Efavirenz was specified and documented.

QC testing was conducted as specified in the relevant specification and according to documented test methods.

HPLCs were used for assay and RS testing of the Efavirenz API. HPLC and GC were networked using suitable software.

The computer access control, authorization of the functions and testing method validation were spot checked during the inspection. SOPs for the management of the Chromatography workstation, which specified the operating procedure and the privilege of the Administrator, manager, analyst, chemist, guest, and a SOP for assessment for the system suitability of Chromatographic were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding data management and analytical method validation were addressed by the manufacturer to a satisfactory level.

Validation of analytical procedures

Analytical protocol validation protocol and report of Efavirenz assay were reviewed and discussed during the inspection.

Stability monitoring of APIs

Requirements for stability monitoring were suitably described in a documented procedure and included ongoing stability.

Chambers for stability monitoring were situated in a dedicated room as part of QC Laboratory 2. Large modern chambers at different temperature/relative humidity settings and one for back-up were

available. Parameters were measured by recorders for each chamber and these were appropriately checked. The chambers were provided with UPS and linked to the company's back-up generator. The chambers were alarmed, including by SMS sent to defined people. The alarm system was checked regularly.

The sample of stability records for Efavirenz API appeared satisfactory.

Stability study followed a SOP for product stability study system. At least one batch of each API product 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. Access to this area was restricted. A sample of each batch of API manufactured was kept. Retention samples were stored in container systems that were comprised of the same materials as those used for the final API.

Handling of out of specification (OOS) results

The OOS/OOT handling procedure was reviewed and discussed.

Microbiological testing

The microbiology laboratory was part of a QC Laboratory. The laboratory was modern, well equipped and staffed by a group of people including microbiologists.

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 cleanroom was conducted according to documented procedures. These were reviewed during the inspection and generally found satisfactory. The results of water testing and environmental monitoring appeared to be satisfactory.

11. Validation

Validation policy

Validation policy for Efavirenz was described in a VMP with validation management described in a SOP. A validation committee with defined members had been formed to coordinate validation activities, with the Quality Director being ultimately responsible.

Validation documentation

The validation protocol and report for Efavirenz process validation was reviewed during the inspection. The protocol required a risk assessment to be performed to determine the level of risk to product quality and described validation requirements for each process satisfactorily.

A new dryer installed in 2014 was selected for detailed inspection. Requirements for DQ, IQ, OQ and PQ were described and associated records were generally satisfactory. PQ was described in a protocol and a report. Three consecutive batches were included in PQ with temperature distribution being

measured by probers distributed throughout the dryer according to a documented matrix. Acceptance criteria were clearly defined and the results indicated that all had been met.

Qualification

Equipment qualification requirements were described in the VMP for Efavirenz. A SOP for equipment qualification operation procedure was reviewed. The equipment requalification was performed every 5 years.

Qualification report of a centrifuge used for final step of Efavirenz API was also reviewed.

Approaches to process validation

Process validation was required to be either prospective or concurrent.

Periodic review of validated systems

The status of validated systems was considered annually during Product Quality Review. In addition the need for revalidation after e.g. process or major equipment change, was defined.

Cleaning validation

Cleaning validation was included in the VMP for Efavirenz. This was not reviewed in detail as Efavirenz API synthesis takes place in facilities dedicated to this API.

Validation of analytical methods

Analytical protocol validation protocol of Efavirenz assay and the report were reviewed (see above QC section).

12. Change control

Change control was managed according to a SOP. A CC regarding production location and process change was reviewed. Non-compliance observed during the inspection that was listed in the full report regarding change control was addressed by the manufacturer to a satisfactory level.

13. Rejection and re-use of materials

Rejection

Rejected materials were suitably labelled and required to be placed in locked designated areas before determining disposition. Arrangements appeared to be satisfactory.

Reprocessing

Reprocessing was permitted and was handled according to a SOP. An example of reprocessing was reviewed and was satisfactory.

Reworking

Rework was not permitted.

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 a solvent recovery were selected for review and generally found satisfactory.

Returns

Returns were handled according to a documented procedure that required a risk assessment to be performed by the QA Manager and approved by the Quality Director. Options for disposition were defined.

14. Complaints and recalls

Complaints were handled according to a SOP with responsibilities clearly defined and complaints classified as either serious or minor, with definitions of each. A risk assessment was required to be performed. Other batches and the need for possible recall were considered.

Annual log books of quality related complaints were maintained and those for 2014 and 2015 were reviewed. Non-compliance observed during the inspection that was listed in the full report regarding complaints was addressed by the manufacturer to a satisfactory level.

A SOP described requirements for API recall. 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.

15. Contract manufacturers (including laboratories)

There was no contract manufacturing of Efavirenz API or key starting materials.

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. Efavirenz APIMF283 and Intermediate (S)-5-chloro-_-(cyclopropylethynyl)-2-amino-α-(trifluoromethyl)benzyl methanol (EV-1) for Efavirenz APIMF253 manufactured at Zhejiang Jiangbei Pharmaceutical Co., Ltd. located at Dongdai Zhang'an Street, Jiaojiang District, Taizhou City, 318017, Zhejiang Province, 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-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