World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the FPP manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer and address	Instituto de Tecnologia em Fármacos (Farmanguinhos) AV. Comandante Guaranys n°447, Curicica, Rio de Janeiro, RJ, Brasil, CEP 22775-903 Phone (55) 21 33485050 Fax: (55) 21 3348-5097 www.far.fiocruz.br Latitude: -22.951386520511914 Longitude:-43.3709740000002
Corporate address of manufacturer	As above
Inspected site	
Address of inspected manufacturing site	As above
Unit / block / workshop number	Building No 70
Inspection details	
Dates of inspection	25 - 27 April 2018
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Manufacture including production, quality control and release of: • Tablet • Coated tablet • Capsule hard Including penicillin's
General information about the company and site	Farmanguinhos was established in 1956 at Maralogia Institute. In 1970 Farmanguinhos became part of Fiocruz under the name of "Drug Production Institute" (Instituto de Produção de Medicamentos – IPROMED in Portuguese). In 1971, IPROMED became one of the laboratories of the "Official System".

In 1976 through Presidential Decree No. 77481 IPROMED gave rise to two technical units, of which one was Drug Technology Laboratory - Farmanguinhos.

In September 1988 by Fiocruz presidency Act No. 152/88 Farmanguinhos became a technical-scientific unit which scope is directly related to the areas of Fiocruz.

In 2004, the Ministry of Health relocated Fiocruz/Farmanguinhoson the campus of Jacarepaguá called Medicines Technological Complex in (Complexo Tecnológico de Medicamentos – CTM in Portuguese).

Farmanguinhos is a non-profit unit of FIOCRUZ.

The Institute carries out its main activities at the Medicines Technological Complex campus (Centro Tecnológico de Medicamentos – CTM in Portuguese) located at Av Comandante Guaranys, 447 in Jacarepaguá – Rio de Janeiro, a 40,000 m^2 building which is divided into:. Industrial plants:

- Building 70 - production of oral solid dosage forms, including antiretroviral drugs Building 40 - production of penicillin's
- Building 10 - laboratories and administrative area.

Amongst the products manufactured by Farmanguinhos are drugs for endemic diseases such as malaria and tuberculosis; antianemic, antiretroviral drugs for the treatment of HIV; anthelmintic, central nervous system, antiretroviral, hypertension and recently immunosuppressive medicines.
In 2012, the Institute incorporated in its portfolio Tacolimus and Pramipexol medicines as a result of the first Partnerships for Productive Development (PDPs). At the Farmanguinhos plant, the Tacrolimus project is in the pilot stage of batch manufacturing and with the secondary packaging of Pramipexol concluded.

In addition, the Institute is involved in research and development activities (R & D) and offers Post-Graduate and Professional Masters courses.

History of previous inspections by national medicines regulatory authorities

This was the second WHO inspection.
The site was inspected/audited by the following authorities:

Authority	**Date/s of inspection**	**Scope of inspection**	**Facility/block/unit covered by inspection**
ANVISA/ SUVISA-RJ Inspection	16 to 20/10/2017	GMP (ANVISA, regulation RDC 17/2010).	building nº10 building nº70 building nº40
ISO	17 to 18/10/2016	ISO 9001:2008	Quality Management System
ISO	05/03/ 2015	ISO 14000:2004	Environment Management System
ANVISA/ SUVISA-RJ	04 to 07/08/2014	GMP	building nº10 building nº70

	Inspection		(ANVISA regulation, RDC 17/2010).	building nº40

Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	See Part 2 below
Restrictions	N/A
WHO product numbers covered by the inspection	Anti-malaria medicines

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
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
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
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
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
WS	working standard

Part 2	Brief summary of the findings and comments

Brief summary of the findings and comments

The inspection focussed on the on-site review of the CAPAs implementation following from the previous inspection.

1. Pharmaceutical quality system

Principle

Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and the results taken into account in batch release; regular reviews of the quality of pharmaceutical products were conducted.

Data integrity

The SOP "Data integrity management" was briefly discussed. SOP was applicable to all technical and administration areas, for example:

- Manufacturing
- Maintenance
- QA
- QC
- Validation
- Regulatory affaires
- Projects

SOP and explained ALCOA principles.

The SOP "Data integrity in Quality Control" was briefly discussed. SOP was applicable to QA, QC and IT departments. SOP explained data integrity policy related to laboratory instruments.

The SOP "Back-up and restoration of electronic data" was briefly discussed. This was IT department SOP.

These three SOPs were implemented as CAPAs after previous WHO inspection.

Management review

The SOP "Quality management system review and analysis" was briefly discussed. According to the SOP MR should be performed at least twice per year.

Last MR review meeting minutes were briefly discussed.

Vice Director of Quality Management presentation discussed during MR was presented to the inspectors. Presentation was detailed and covered standard agenda and KPIs.

Quality risk management
The SOP "Risk analysis" was briefly discussed. Mainly FMEA with 10 scoring system was used as a RA tool. The SOP was detailed and explained well RA process and its application. SOP was not updated after previous WHO inspection. RA register was available.

A number of RAs were briefly discussed.

Product Quality review
The SOP "Periodic product review" was briefly discussed. The SOP was updated after previous WHO inspection. PQR was performed once in a year according to the date when product was registered with ANVISA; for example registration was in January, review period was January to December. According to the SOP PQR should be completed within 3 months. Minitab was used for statistical evaluation of process capability.

PQR for XX for time period 01/02/2017 to 28/02/2018 was briefly discussed

The SOP "Statistical analysis of PQR using Minitab" was briefly discussed. CpK was used to evaluate process capability.

Complaints and Product Recall
The SOP "Complaints management" was briefly discussed. Complaints investigations were carried out by Customer care service (SAC). Complaints register was available for inspection. Complaints management was carried out using *SoftExpert* Excellence Suite software. According to the SOP complaints should be trended annually. Trends from 01/04/2017 till 31/03/2018 were briefly discussed.

A number of complaints were briefly discussed.

The SOP "Product recall" was briefly discussed. Recalls were managed by the committee what consisted of the Technical manager, Regulatory Affairs (SAR) and GQL. Recall classification was following:

- Class I – medicine may cause damage to health, resulting in death, threat to life of permanent damages, ANVISA should be informed and recall initiated within 48 hours from time of detection of defect
- Class II – medicine may cause temporary damage to health or damage reversible with treatment, ANVISA should be informed and recall initiated within 48 hours from time of detection of defect
- Class III – medicine may bring adverse consequences to health

SAR was responsible to inform ANVISA. In case if no real recall was executed within 12 month, mock recall should be carried out. Last Class II mock recall was performed December 2017.

Returns
The SOP "Returned products" was briefly discussed. It was explained that till the date of inspection there were no returned products.

Self-Inspection

The SOP "Self-inspection" was briefly discussed. Requirements for selection of internal auditors were specified. Qualified auditors were involved only in self-inspections and supplier qualification. List of qualified auditors and self-inspection schedule for 2018 was presented to the inspectors. Data integrity topic was included in all department audit schedule.

According to the SOP self-inspection was performed at least once per year. Self-inspection outcome was described in the Report. Non conformities were classified as per the SOP "Non-conformities":

- Critical
- Major
- Minor

Audit plan for QCL laboratory and report were briefly discussed. Self-inspection of QCL department was carried out from XX. CAPAs were proposed by the auditee department and evaluated by lead auditor. If necessary follow-up inspected was carried out. SoftExpert Excellence Suite software was used to manage self-inspections.

Change controls

The SOP "Change control" was briefly discussed. CC register was presented to the inspectors. The SOP was applicable, but not limited to facilities, production utilities, equipment and instruments, computerized systems, cleaning, suppliers, documents. *SoftExpert Excellence Suite* software was used for change management.

A number of CCs were discussed.

Deviation management

The SOP "Deviation management" was briefly discussed. The SOP was applicable, but not limited for RA, QC, production, complaints, maintenance, utilities, warehouse, self-inspection QA. QA department was responsible for dealing with deviations. Deviations were managed by SAP system. Deviations were classified based on risk assessment.

The SOP explained root cause analysis. Two tools were used, Ishikawa diagram and 5 WHYs. Deviations trend analysis was carried out every three months. According to the SOP root cause investigation should be carried out within 30 days. Deviation register and trends were presented to the inspectors. Deviation investigation printout from SAP system was attached to the batch production records.

A number of deviation investigations were briefly discussed.

Corrective and preventive actions

The SOP "CAPA management" was briefly discussed. The SOP was applicable, but not limited for deviations non-conformities, deviations, risk analysis, internal and external inspections, complaints etc. CAPAs were managed by SAP system.

Documentation system
Documents were designed, prepared, reviewed and distributed according to written procedures. Documents were approved, signed and dated by the appropriate responsible persons. Documents had unambiguous contents: the title, nature and purpose were clearly stated. Documents were regularly reviewed and kept up to date. QA department was of charge of document management. Quality Manual was available.

The SOP "Quality documentation system" was briefly discussed. According to the SOP documents should be reviewed at least every 3 years or whenever there are any changes. Distribution of the documents was controlled manually. Documents versions, elaboration and approval were controlled by the SAP system.

The SOP "Receipt, distribution and release of materials and products" was briefly discussed.

The SOP "Data integrity – quality control" was briefly discussed. This SOP was applicable for data review. Check list was used for audit trail review.

The SOP "Batch records review" was briefly discussed. This SOP was applicable to batch production, packaging records review and quality control data review. This SOP was QA document. Check list was used for documents review. Final product release was carried out by QA senior analysts. Release was done by SAP system.

Supplier's qualification
The SOP "Qualification of suppliers" was briefly discussed. The SOP was applicable for raw materials, packaging materials suppliers and service providers. Supplier's qualification was carried out by team of trained auditors from the QA department.

A supplier qualification program was described in SOP "Supplier Technical Qualification" and in SOP "– External Quality Audits.

The quality of the incoming materials was monitored through the quality control results (physical-chemical and microbiological tests) and production performance. The performance of the suppliers / manufacturers was evaluated based on the results of the evaluations carried out by the Quality Management Coordination. In case, any problems were found related to the quality of the products, re-audits were carried out annually
The list of qualified suppliers was available.

2. Personnel
Farmanguinhos had sufficient number of qualified personnel to carry out the tasks for which the manufacturer was responsible. Farmanguinhos had an adequate number of personnel with the necessary qualifications and practical experience. Eating, drinking, smoking, jewellery, cosmetics and personal medicines were not allowed in production and QC areas. Persons having an apparent illness or open lesions were not allowed to handle starting materials, packaging materials, in-process materials. Medical checks were carried out once per year.

Key Personnel
Managerial responsibilities were described in the position job descriptions.

The following job descriptions were checked:
- Software administrator
- Software coordinator

Training
The SOP "Training" was briefly discussed. The following training modules were available:
- Induction training – information about organization, internal rules, safety, general GMP
- Job related procedures training (theoretical)
- Practical training

Training effectiveness was evaluated by written tests (open questions and multiple choice questions).

Individual and departments training schedules for 2017 and 2018 were presented to the inspectors. Trainings performed in 2017 in the different departments were briefly discussed.

Training records and personal file of: XX, operator in the dispensing and area as well as that of YY, supervisor, were reviewed.

3. Production system

Production operations followed clearly defined procedures in accordance with manufacturing and marketing authorizations. Deviations were approved in writing and investigated. Checks on yields and reconciliation of quantities were carried. Operations on different products were not carried out simultaneously or consecutively in the same room.
Pressure differentials during inspection were controlled using portable instruments. However permanent devices were installed but not yet in use.

Dispensing was carried out in two separate dispensing booths. One was dedicated for dispensing of APIs and one was dedicated for dispensing excipients. The SOP "Receipt, dispensing and return of materials to the warehouse" was briefly discussed.

Primary packaging lines were connected to the secondary packaging lines. Secondary packaging lines were well separated.

Batch processing and packaging records
Batch processing and packaging records of validation batch were briefly discussed.

Sampling and testing

The following SOPs were briefly discussed:

- "Raw materials sampling" ,
- "Cleaning of sampling rooms "
- "Receiving of Material and products "
- "Sampling of Packaging material"
- " Inspection of products received"

Identification tests for products under WHO prequalification were performed of each container of starting materials.

3. Facilities and equipment system

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Access to the production premised was restricted to authorized persons. Change rooms doors were interlocked.

Computerized systems validation

Computerized system VMP was briefly discussed. VMP was revised once per year.
Validation master plan for computerized system was briefly reviewed. Validation status was revised every 3 years. In case there were changes or malfunction of the equipment re-validation was carried out.

Production process validation

Process validation was ongoing, in order to include the coating process performed on site. The manufacturing process of the first validation batch was currently undergoing primary and secondary packaging. The manufacturing process of the second validation batch was undergoing compression on the date of the inspection.

Cleaning validation

The SOP "Qualification of cleaning" was briefly discussed. Worst case was based on solubility, toxicity and difficult to clean. Cleaning validation protocol / report for the tablet coating machine and one of the tablet press machines used for XX production was briefly discussed.

Clean equipment hold time validation studies were carried out for the same three consecutive batches used for cleaning validation. Clean hold time was established by total microbial counts. Tests were carried out after cleaning and after 7 days. Action and alert limits were specified.

Utilities

HVAC system

XX AHUs were installed for block 70. A number of AHUs re-qualification protocols/reports were briefly discussed.

AHUs qualification was contracted out and performed once per year
Pressured differentials between filters was controlled and recorded once per week.

AHU monitoring BMS system was under qualification. DQ, IQ and OQ stages were completed. Alarm system was installed; performance will be checked during PQ stage.

Purified water system (PW)

PW systems were different for penicillin's block and general block.

New PW system was installed September 2017. DQ, IQ and OQ stages were completed. During inspection PQ was in Phase 3, what will be finished December 2018. PW was produced by two Reverse Osmosis units.

Phase I test period was for 22 working days and Phase II for 20 working days. PW tank and pipes were made from stainless steel 316L. Materials certificates were presented to the inspectors. Orbital welding was used, welder's certificate was available. Endoscopic welding videos were available for 20 % of welds.

Samples from all sampling points were collected and analysed daily during Phase I and Phase II. Alert and action limits were specified.

A number of parameters of the PW system were monitored on line.

Compressed air system

Compressed air system layout was briefly discussed in relation with the compressed air supplied to the coating equipment. Compressed air analysis was carried out annually for all user points and sample from generation system. Tests were carried out according to the ISO 8573 standard.

Laboratory equipment

Generally the laboratory had test equipment, instruments and other devices for the performance of the tests and/or calibrations, validations and verifications. Calibration status labels were attached to instruments. All laboratory instruments had "instrument log books".

Laboratory equipment Qualification / verification / preventive maintenance schedule was presented to the inspectors.

4. Laboratory control system

Laboratory equipment and instruments were suited to the testing procedures undertaken. Laboratory had adequate facilities, trained personnel and approved procedures for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and for monitoring environmental conditions.

The SOP “Instruments access control and privileges” was briefly discussed.

The SOP “Atypical or OOS results management” was briefly discussed. The SOP was applicable for Physico–chemical analysis and microbiological analysis and was based on ANVISA guideline, similar to MHRA guideline. System suitability failure was considered as OOS and investigated in accordance to the SOP.

The SOP “Good chromatographic practice” was briefly discussed.

The SOP “Stability studies” was briefly discussed.

The SOP “Reference and working standards management” was briefly discussed. Working standards (WS) were qualified against reference standards. WS were dispensed in amber colour vials.

The SOP “Retention samples management” was briefly discussed. SOP was applicable for APIs, excipients, finished products. APIs samples were retained for 4 (3 years expiry date of finished products + 1 year), finished product samples were retained expiry date + expiry date.

Microbiological laboratory
Microbiological laboratory was separated from chemical laboratory and production. Work with Master Strains and analysis was carried out in different LAF cabinets.

The SOP “Environmental monitoring” was briefly discussed. Passive and active air sampling was used. Action and alert limits were specified based on historical data. EM results were presented to inspectors.

In the Microbiology Laboratory reference cultures were obtained from the Institute Micro Biologics. The strains were originally derived from ATCC strains. Maximum 5 passages were used.

Medias were sterilised following manufacturer’s instructions 121 C for 15 minutes.

Growth promotion test was performed on each batch of dry media. Sterility test, positive and negative controls were performed on each Media prepared in the laboratory.

5. Materials system

Raw materials were stored in warehouse leading to the production block. Materials management was done manually and by SAP system for the raw materials and packaging materials. Finished products were managed through SAP only. Sampling of raw materials was done in one sampling room under LAF. Sampling room usage log book was presented to the inspectors. Sampling of primary packaging was done in the warehouse in a dedicated sampling booth.

6. Packaging and labelling system

The SOP “Product packaging” was briefly discussed. The SOP was applicable for secondary packaging operations, including labelling. Line clearance was carried out according to the check list which was part of the batch processing and packaging records.

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 **Instituto de Tecnologia em Fármacos (Farmanguinhos), located at AV. Comandante Guaranys n° 447, Curicica, Rio de Janeiro, RJ, Brasil, CEP 22775** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products.

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 pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. 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/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. 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

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
   Short name: WHO TRS No. 961, 957), Annex 1
   http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
    ***Short name: WHO TRS No. 961, Annex* 9**
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
Short name: WHO TRS No. 943, Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
Short name: WHO TRS No. 961, Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
Short name: WHO TRS No. 981, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
Short name: WHO TRS No. 981, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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. Fiftieth 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. Fiftieth 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. Fiftieth 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

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
Short name: WHO TRS No. 996, Annex 3
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