

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

Part 1	General information
Manufacturers details	
Company information	
Name of manufacturer	Aurisco Pharmaceutical Co., Ltd.
Corporate address of manufacturer	Badu Industrial Park Zone, Tiantai, Zhejiang Province, 317200, P.R. China
Inspected site	
Address of inspected manufacturing site if different from that given above	Badu Industrial Park Zone, Tiantai, Zhejiang Province, 317200, P.R. China GPS: 29.118706 N, 121.055335 E DUNS: 545319522
Unit / block / workshop number	Workshop 805
Manufacturing license number	ZHE 20050429
Inspection details	
Dates of inspection	29 January -1 February 2018
Type of inspection	Follow up inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of APIs and intermediates
General information about the company and site	Aurisco Pharmaceutical Co. was founded in 2002. The company has three production sites. The site in Zhejiang Tiantai subjected to this inspection is located in Badu Industrial Park Zone. The site is surrounded by light industry. There are no other chemical or pharmaceutical manufacturers in the immediate vicinity. This site produces Tenofovir Disoproxil Fumarate and its intermediate PMPA in workshop 805. It also supplies intermediates to other API synthesis companies. The site also produces several steroidal APIs which are manufactured in a separate workshop.
History	This was the second WHO inspection of the Tiantai site. The previous inspection was conducted in April 2017. The site was inspected by USFDA in 2013 and Behörde für Gesundheit und Verbraucherschutz der Freien und Hansestadt Hamburg, Germany in 2016 with positive outcomes, however to note that the product scope and production blocks involved in those inspections were different to the WHO inspection.

Aurisco Pharmaceutical Co, Badu, Tiantai, China
29 January – 1 February 2018

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Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	This was a follow up inspection to the April 2017 inspection which focused on the issues arising from the previous inspection as well as the production and control of Tenofovir Disoproxil Fumarate in Workshop 805. The inspection covered checking the CAPAs implemented following the critical and major deficiencies observed in the aforementioned WHO inspection as well as following sections of the WHO GMP text i.e. • 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) Areas visited: • Warehouses • Workshop 805 • QC labs
Restrictions	NA
Out of scope	API products other than Tenofovir Disoproxil Fumarate (APIMF320) manufactured on this site were outside the scope of this inspection.
WHO product numbers covered by the inspection	Tenofovir Disoproxil Fumarate (APIMF320)

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

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	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
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1. Quality management

A formal documented system for quality assurance was established, with procedures covering all key quality elements being in place. Operations were specified in a written form and 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 appropriately specified in written job-descriptions. Product and processes were monitored, and these 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 company organization and key staff including General Manager, QA Vice General Manager and QA Director have been changed since the last inspection. The Quality Unit was divided into QA and QC, which was managerially separate from the production department. At the time of the inspection, the post of QA manger was vacant and it was planned for the post to be filled later during February 2018.

The Production VP had overall responsibility for managing production activities and there was a manager for each of the production Workshops. Responsibilities were described in the relevant job descriptions for the key personnel.

Internal audits (self-inspection)

Internal audit was not reviewed in detail during this inspection.

Product quality review (PQR)

PQRs were performed according to an SOP. It was required that PQRs be done annually using data from all batches of APIs produced during the review period. The SOP specified the review of intermediate and API test results, OOS batches, deviations, changes, stability monitoring, returns, complaints and recalls.

The Tenofovir Disoproxil Fumarate (B2) PQR for 2017 was reviewed. There was one OOS batch, no complaints and no returns. There were two batches manufactured in 2016 that had been recalled due to contamination issues discovered in the last inspection. TDF B2 was released in 6 different quality grades all produced by a single process.

PMPA, an intermediate of TDF B2 was supplied to outside API manufacturers as a commercial product. The PMPA 2017 PQR was also reviewed.

Quality Risk Management

A Quality risk management procedure was revised and the FMEA tool for quality risk management had been established. The FMEA model and an associated template had been introduced since the last inspection.

The risk assessment report for cross contamination for Workshop 805 with risks from other workshops was reviewed. The controls in place and monitoring results of steroid residues appeared satisfactory.

Management review

An SOP had been implemented since the last inspection. The procedure requires review and the summarization of separate reviews of CAPA, Audits and Customer Feedback, PQRs, EM, Deviations and OOS.

Deviations

Deviations were handled according to written procedures. Deviations were classified into critical and non-critical as per the SOP. A deviation regarding the B2 OOS bath was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding deviation management, were addressed by the manufacturer to a satisfactory level.

2. Personnel

Personnel qualifications

At the time of the inspection 388 people were employed. There appeared to be a sufficient number of personnel who were qualified through qualifications, experience and training. There was a training programme in place in support of routine GMP training.

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.

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 were spacious to allow placement of equipment.

The chemical and clean area in Workshop 805 were inspected. Workshop 805 included a general chemical synthesis area and a clean area (classified as Grade D) for crystallization, harvesting and packaging – the latter not dedicated to only B2 API's.

The design of the rooms, placement of equipment and maintenance thereof appeared suitable for the processes involved with the synthesis of B2.

Since the last inspection, a new API pilot batch, an B2 analogue was manufactured in Workshop 805.

HVAC System

A 100% fresh air HVAC system was used in Workshop 805 clean area. Workshop 805 was stated to have a dedicated AHU equipped with G3 Prefilter, F5 Filter and HEPA final filters.

Water system

Purified water (PW) was not used in the final purification stages of the API manufacturing but for equipment washing. The system was designed using double reverse osmosis to produce purified water. The PW generation system was linked to two distribution loops, one was dedicated for Workshop 805 (B2 line) and the second for all other workshops. This system remains the same as at the last inspection.

Containment

The final synthesis, purification and packaging of B2 API took place in a non-dedicated facility shared with other products. The workshop is well segregated from those producing steroidal APIs.

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 B2 API appeared to be of appropriate design and size for its intended use, cleaning and maintenance.

Equipment maintenance and cleaning

In general equipment and facilities look well maintained.

The maintenance program for 2017, Workshop 805 was reviewed. There were monthly and quarterly schedules in place. Reactors in chemical area was made with glass lined inner surface and those in clean area from stainless steel. Glass lined reactor integrity tests were performed regularly, as well as being entered via the manway for visual examination.

Calibration

Measuring equipment was required to be labelled with its calibration status and all examples viewed were within date. There was an annual schedule in place and instruments were mainly calibrated in-house but with some work performed under contract with the provincial metrology service.

Computerized systems

Computerized systems were not used for material or production control but used in QC lab for HPLC and GC networking.

5. Documentation and records

Documentation system and specifications

Documents were managed according to an SOP. Activities were documented in SOPs and other appropriate documents such as batch manufacturing records (BMRs) and logs. Those reviewed were seen to be appropriately approved and version controlled. All records and other documentation requested during the inspection were promptly available following request.

Master production instructions (master production and control records)

Approved master production instructions were available. For the production of all grades B2 only one Master Batch Record was used.

Laboratory control records

Laboratory logs were in place for receipt of samples and appropriate testing records were seen to be kept and were available for review.

Batch production record review

Several batches of productions records for B2 were reviewed and discussed. A batch production record, together with the deviation and OOS investigation file were reviewed. Non-compliances observed during the inspection was listed in the full report regarding records and BMR design and use were addressed by the manufacturer to a satisfactory level.

6. Materials management

General controls

Manual systems were in place for the receipt and tracking of inventory. Raw materials and finished goods were stored in a dedicated area of the warehouse. There was a tank farm for the receipt of solvents and other liquid reagents as well as an external drum store. These appeared to be tidy, well managed and appropriately labelled.

Receipt and quarantine

Solid materials were required to be checked on receipt, including for damage and verifying that the supplier was approved. They were placed in quarantine and labelled with the storage location. Bulk liquids were received from either dedicated tankers or tankers accompanied by a cleaning certificate.

Sampling and testing of incoming production materials

Production materials were sampled by QC in a designated sampling area according to a defined sampling plan. After testing by QC, materials were released and an appropriate status label was attached to each container. Records viewed appeared satisfactory. There were two sampling rooms used for raw material sampling, one for steroids and another for other materials.

Storage

The B2 API was stored in 2 to 8°C cold storage. Temperature was controlled and monitored.

7. Production and in-process controls

Production operations

Synthesis and production of B2 with a validated batch size took place in Workshop 805 chemical area. Final purification, crystallization, drying and packaging was performed in the clean area. The intermediate PMPA used in house and for selling were also manufactured in the chemical area. There were 6 different quality grades of B2 manufactured using a single process. There were two crystallizers in the clean area with one dedicated to crystallization of B2.

In-process sampling and controls

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

Blending batches of intermediates or APIs

Blending of B2 was permitted with the expiry of the shortest expiring batch retest date allocated to the blended batch. The blending validation protocol and report for B2 were reviewed and acceptable.

Contamination control

B2 API synthesis, purification, crystallization, drying and packaging was performed in non-dedicated facilities. Adequate precautions to minimize the likelihood of contamination, including final stages taking place in a Grade D controlled environment, were in place. Cleaning procedure for equipment had been validated. Final crystallization is performed from non-aqueous media in stainless steel reactors to limit risks of glass and microbial contamination.

8. Packaging and identification labelling of APIs and intermediates

Packaging materials

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

Packaging and labelling operations

An area in the warehouse where relabeling was performed was inspected. The corrective action to the observations regarding the labelling and records of the labelling operation from the last inspection had been put in place.

9. Storage and distribution

Warehousing procedures

Finished APIs were stored in a designated warehouse and held in quarantine until released by an authorized person.

Distribution procedures

APIs and intermediates were released for distribution after release by the Quality Unit. A product release SOP was reviewed and discussed. B2 API release specifications for different markets with different quality grades, prior to batch release were verified.

10. Laboratory controls

General controls

The company had an organized and suitably equipped QC laboratory for API testing.

Testing of intermediates and APIs

The sample receiving, and distribution procedure and log books were inspected. Samples for testing were kept in a designated area. Non-compliances observed during the inspection that was listed in the full report regarding the sample receipt, recording and tracking were addressed by the manufacturer to a satisfactory level.

QC testing was seen to be conducted as specified in the relevant specifications and according to documented test methods. Agilent HPLC and GC were used for testing of B2 API. The HPLC and GC were networked and OpenLab software installed. The computer access control, authorization of the functions and testing method verification were spot checked and appeared to be acceptable.

Characterization of WRS

Secondary reference standards were prepared against the primary reference standards according to an SOP and were periodically requalified. The characterization record of a WRS batch was reviewed. The retesting time of the working reference of B2 API was documented.

Stability monitoring of APIs

Requirements for stability monitoring were described in a documented procedure which included ongoing stability. Chambers for stability monitoring were situated in a dedicated room within the QC Laboratory. Chambers for the applicable temperature/relative humidity requirements for ICH and WHO regions were available. Parameters were measured by recorders for each chamber which were periodically checked. The chambers were provided with UPS.

The stability sample and records for B2 API for the validation batches and ongoing batches appeared satisfactory and reconciled.

Reserve/retention samples

B2 API samples were stored in 2-8°C refrigerator which was located in an access control room. A sample of each batch of API manufactured was kept. Retention samples were stored in containers that were comprised of the same materials as those used for packaging of the final API.

Handling of out of specification (OOS) results

The OOS/OOT handling procedure was reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding the OOS investigation procedure were addressed by the manufacturer to a satisfactory level.

Data management

The company had basic data integrity controls in place. The Waters Chromatographic data system, risk assessment of the archival, back up strategies and associated data life cycle risk were inspected. Data management for the stability monitoring system was inspected. Non-compliances observed during the previous inspection were satisfactory addressed.

11. Validation

Validation policy

Validation policy for B2 was described in VMP with Validation Management described in a written procedure.

Process Validation

Process validation of B2 remains the same as per the previous inspection. Since the previous inspection, additional process validation which include drying, blending and solvent recovery have been performed and was considered acceptable.

Qualification

Equipment qualification requirements were described in the VMP. Equipment performance qualification in Workshop 805 were reviewed together with process validation and considered acceptable.

Cleaning validation

Since the previous inspection, trial batches of a new B2 analogue has been produced in Workshop 805 which shared the B2 equipment in the chemical area. A cleaning validation SOP and cleaning validation report were reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding cleaning validation were satisfactory addressed by the manufacturer.

Validation of analytical methods

A compendial analytical method was used for B2 API testing. Analytical method validation for B2 residue testing was reviewed and considered accepted.

Computerized system validation

Update of the software of the QC HPLC and GC instruments by installation of OpenLab was briefly reviewed. The system was qualified by Agilent with the records signed off by the QA group.

12. Change control

Change control was managed according to an SOP. Changes were classified into critical and non-critical. Several change controls were reviewed and discussed during the inspection. Non-compliances observed during the previous inspection were satisfactory addressed by the manufacturer.

13. Rejection and re-use of materials

Rejection

The register was available and reviewed.

Reprocessing and reworking

Reprocessing and reworking procedure were available and reviewed.

Recovery of materials and solvents

A solvent recovery procedure was reviewed which allowed for the recovered solvents to be used in the same or different processes based on assessment and approved from QA. Recovered solvents are used in the upstream process but not used in the final purification stage.

14. Complaints and recalls

A procedure was in place. No complaints had been received for B2 API since the last inspection. The two contaminated batches identified during the previous inspection was recalled.

15. Contract manufacturers (including laboratories)

No contract manufacturers or contract laboratories were used for routine production and testing. X-ray diffraction testing of B2 polymorph was contracted out during R & D and for validation purposes.

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 ***Aurisco Pharmaceutical Co., Ltd. located at Badu Industrial Park Zone, Tiantai, Zhejiang Province, 317200, P.R. China,*** 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 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