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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Changzhou Yabang-QH Pharmachem Co. Ltd.
Corporate address of manufacturer	18 Jinlong Road, Chunjiang Town, Xinbei District, Changzhou, Jiangsu. P. R. China 213127
Inspected site	
Address of inspected manufacturing site if different from that given above	DUNS 527929456 Latitude 31.9744N Longtitude 119.9663E
Unit / block / workshop number	Plant 1, Plant 3 Line 1 and Plant 3 Line 2
Inspection details	
Dates of inspection	4 to 7 July 2016
Type of inspection	Routine
Introduction	
Brief summary of the manufacturing activities	Manufacture of APIs and API intermediates for human and veterinary use.
General information about the company and site	The company was established in 2004 to make anthelmintic APIs. Products at the time of the inspection were anthelmintic and antifungal APIs and high value intermediates.
History	Previous WHO Inspection 16th to 18th September 2013. EDQM 20th to 22nd April 2015 CFDA 24th to 25th March 2014 CFDA 24th to 26th March 2016 Ministry of Agriculture 10th to 11th June 2015.
Brief report of inspection	

activities undertaken	
Scope and limitations	
Areas inspected	• 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) Site visit: Warehousing, (solids RMs, tank farm, Finished Goods, Packing Materials, Production Cartridge Filters, Maintenance Spares), Plant 1 and Plant 3, Purified Water System (Plant 1 and plant 3), QC labs
Restrictions	NA
Out of scope	Plants 2 & 5 were outside the scope of the inspection.
WHO product numbers covered by the inspection	Mebendazole API (APIMF 220)

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 with management responsibilities shown in an approved organization chart. Responsibilities were suitably described, including in position descriptions for key staff. The position descriptions reviewed were acceptable. The responsibilities of the Quality Director included all those topics specifically stated in the WHO Guidelines. The Quality Director reported to the General Manager and was responsible for supervising the QA and QC managers. In the absence of the Quality Director, the QA Manager would act as deputy.

Responsibility for production activities

The structure and management responsibility for production activities was shown in an approved organization chart. Responsibilities were suitably described, including in position descriptions for key personnel. The position descriptions reviewed were acceptable.

Internal audits (self-inspection)

Not covered by this inspection.

Product quality review

The product quality review was performed according to a SOP. PQRs of Mebendazole were conducted on a yearly basis. Plant 1 and Plant 3 reviews were conducted separately.

Mebendazole PQR 2013 for Plant 1 and Plant 3 were reviewed. There were no rejected raw materials, packing materials, batches of APIs and no complaints or returns of Mebendazole APIs.

PQR of Mebendazole 2014 in Plant 1 and Plant 3 were also reviewed. No product return or recall occurred. The major change was to introduce a new production line in Plant 3. This was reviewed.

PQRs of production in 2015 showed all details to be satisfactory. Non-compliances observed during the inspection, that were listed in the full report regarding PQR, were addressed by the manufacturer to a satisfactory level.

Quality risk management

There was a written procedure for Quality risk management. Various approaches to risk assessment were allowed. The risk management had not been fully implemented at the time of inspection. Non-compliances observed during the inspection, that were listed in the full report regarding quality risk management, were addressed by the manufacturer to a satisfactory level.

Deviation

Procedure for Handling Deviation was reviewed. There were two types of deviation, critical and non-critical, mentioned in the procedure. Deviations in 2015 were reviewed. Non-compliances observed

during the inspection, that was listed in the full report regarding deviation, were addressed by the manufacturer to a satisfactory level.

2. Personnel

Personnel qualifications

There were sufficient personnel who were suitably qualified through qualifications, experience and training. 327 persons were employed by the company at the time of inspection.

Job Description, Preparation and Management were described in an SOP. All employees and contractors were covered. Responsibilities were well described, including position descriptions for all personnel. Position descriptions for selected key staff were reviewed and generally found satisfactory.

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. Photographs of the requirements were on display.

Training

Training was performed according to an SOP. All employees were covered. QA & HR would check the qualifications of trainers. For new employees, the relevant department and QA would give the training requirements to HR. New employees were issued with a company handbook which included legal requirements. The training plan for 2015 of a process operator in Plant 3 was checked and was completed. The company training plan for 2016 was in place.

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. The site was observed to be maintained to a satisfactory standard.

Buildings were constructed of masonry with both internal and external finishes appropriate to the activities conducted. Housekeeping and maintenance were observed to be satisfactory. Where required, flying insect insectocutors, rodent and pest traps/barriers were installed.

HVAC systems

A dedicated HVAC system provided filtered air to supply to the clean area in Plant 3 to meet requirements for Grade D environment for final crystallization, drying and packaging of Mebendazole API. This was a circulatory system with specified make-up.

All filters were monitored using Magnehelic gauges. When readings, showed that the maximum pressure drop had been reached, the filter was changed. No filters were cleaned for re-use after filter is changed. AHU systems were revalidated annually Details were not inspected.

Water system

Purified water was used in the final stages of Mebendazole API manufacture. The system was a design using reverse osmosis and EDI to produce purified water meeting EP and CP specifications. The water system appeared to be well maintained and the results of regular monitoring indicated that it was under control.

The last review of data, available at the time of the inspection, was from 4th January 2015 to 28th December 2015 and was reported in a document. Results from samples were reviewed for microbiological results. All samples showed results <10 cfu/ml. The sampling plan for 2016 was checked.

The final stage Qualification report for the PW system performed during 2014 to 2015 was reviewed and considered acceptable.

Compressed air

Compressed air was used for micronisation of Mebendazole and was reviewed during the inspection.

Computer system

Computer system was used in the QC lab for networking HPLC and GC only.

4. Process equipment

Design and construction

Process equipment in the finishing areas of Plant 1 and Plant 3 were inspected. In all areas, process and utility pipelines were observed to be adequately supported and labeled. Reactor systems were designed for reflux, distillation and stirring operations, as required.

Equipment maintenance and cleaning

Preventative Maintenance of Production Equipment was described in an SOP. This covered all equipment and a maintenance schedule was drawn up. As an example, a maintenance plan for a reactor was reviewed and found acceptable.

Calibration

Instrument/gauge calibration was covered in an SOP. A tachometer on the agitator of a reactor as an example was reviewed. Calibration recheck was due in July 2016.

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). These were approved and version controlled. All records and other documentation requested during the inspection were readily available.

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. An SOP for centrifuge bag cleaning was reviewed.

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 for all production lines used for Mebendazole production.

Batch production records and batch production record review

The batch numbering system was described in an SOP. All raw materials, packing materials, intermediates and finished products were included.

BMRs were available and up to date as reviewed during the inspection. The productions records for a batch of Mebendazole and the associated records for the intermediates used in this batch were reviewed. These records appeared to have been properly completed and reviewed.

Laboratory control records

Laboratory testing records were kept and available in general.

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. Materials were issued in full containers to production according to a Material Request Form. No dispensing was done by warehouse staff.

Receipt and quarantine

On receipt, materials were checked for damage and against the approved supplier list controlled by an SOP. They were labelled segregated and quarantined appropriately.

Sampling and testing of incoming production materials

Materials were sampled by QC following a documented sampling procedure and sampled by QC before release. The containers sampled were labelled with a sampled label. Sampling was described in an SOP.

Vendor approval

Managing the Qualification of Suppliers was detailed in an SOP. All materials were covered and contractors were also included. Suppliers of critical materials (key materials) would be audited. For other materials, a “desk-top” audit would be conducted. Samples would be analysed. The company was understood to have satisfactory agreements with the suppliers.

Storage

Materials were stored in designated warehouses that were generally well organized, clean and tidy. Warehouses were equipped, as required, with proprietary racking. Materials were stored on plastic pallets. Insect and rodent traps etc. were installed, as appropriate. At the time of the inspection, the locked "Reject Area" in Building E was empty.

Warehouse for solid, liquid materials and bulk solvent tanks were inspected and considered acceptable. Mebendazole API product was stored in a warehouse provided with environmental control. Records indicated that the specified conditions had been maintained.

7. Production and in-process controls

Production operations

Production of Mebendazole API took place in the Plant 1 and Plant 3 including chemical synthesis in chemical areas, and purification, drying and packaging in Grade D clean areas.

They were not dedicated to Mebendazole API production. Different grades, of Mebendazole API, including those for human and veterinary use, were manufactured in both plants, by the same process. The specification for WHO grade is the same as EP.

All of the above production areas were inspected and generally found to be of suitable standard, clean and logically organized to suit their intended purpose.

Holding time

A Hold-Time study was conducted before the WHO inspection in 2013. Details were reported in a document. The holding time in routine production was specified and reported.

In-process sampling and controls

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

Blending batches of intermediates or APIs

Blending operation were only performed for tailing material of Mebendazole.

Contamination control

Plant 1 and plant 3 were not dedicated to production of Mebendazole. Adequate precautions to minimize the likelihood of contamination, including final stages taking place in a Grade D controlled environment, were in place.

8. Packaging and identification labelling of APIs and intermediates

Packaging materials

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

Label issuance and control

Labels were printed and issued according to an SOP and were adequately controlled.

Packaging and labelling operations

Packaging and labelling operations were described in batch packaging instructions. Polyethylene bag was used for the primary packing of intermediates and final API.

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.

Finished API products were stored in a temperature-mapped room. Inventory was recorded on QA-issued log sheets.

Distribution procedures

Product release and BPR review was described in an SOP. Product release was the responsibility of QA. The release procedure was comprehensive, including review of BMRs, BPRs, any deviations, OOSs etc., QC results including chromatograms. A final product label was included. Requirements were detailed in a check-list. An example of the release of a recent batch was reviewed and found satisfactory, apart from details on the label.

10. Laboratory controls

General controls

Procedures for sampling, testing and approval were documented. Material and product specifications and laboratory records were maintained

Reference standards

Reference standards were available and used for Mebendazole testing.

Testing of intermediates and APIs

The sample receiving and distribution log book was checked. QC testing was conducted as specified in the relevant specification and according to documented test methods.

Agilent GCs and HPLCs were networked with OpenLab EZchrom software. The computer access, control and authorization of the functions were spot checked during the inspection.

Microbiological testing

The microbiology laboratory was part of QC Laboratory. Media preparation and sterilization were spot checked. Microbial testing procedure for PW was reviewed.

Stability monitoring of APIs

Stability study was managed according to an SOP. Stability chambers were housed in a dedicated room. Included were chambers set to 25 ± 2^0C/60±5%RH and 30 ± 2^0C/75±5%RH used for Mebendazole stability testing. Cabinet logbooks were maintained and stability samples logs recorded the start of the study and when samples were removed. Location parameters were also given.

The data from the chambers was recorded automatically. Print-outs were kept in a logbook. Out-of-range alarms were fitted. Also, the stability chambers were connected to a UPS and the back-up diesel generator.

Reserve/retention Samples

Reserve/retention samples were stored in proprietary draw system in a temperature controlled, dedicated room. As an example, it was requested to look at a Mebendazole batch. The sample was satisfactory. The room was controlled with specified temperature and RH.

11. Validation

Validation policy

Validation policy for Mebendazole was described in VMP and the SOP for process validation approaches was reviewed and acceptable in general.

Qualification

A reactor, as an example of equipment qualification, was reviewed and found acceptable.

Process validation

Documentation (including protocol, report and BMRs) regarding the validation of the Mebendazole process operated in Plant 3 Line 2, was reviewed.

Cleaning validation

Cleaning validation was performed according to an SOP. Cleaning validation protocol and report of a line in Plant 3 were reviewed. Non-compliances observed during the inspection, that were listed in the full report regarding cleaning validation, were addressed by the manufacturer to a satisfactory level.

Computerized system validation

Computer validation for QC software was spot checked. Non-compliances observed during the inspection, that was listed in the full report regarding computerized system in QC lab, were addressed by the manufacturer to a satisfactory level.

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.

12. Change control (CC)

Change control was managed according to an SOP. Major changes made since last inspection related to Mebendazole were documented. The change control log book and several changes, including major changes to introduce a new production line in Plant 3, were reviewed and found acceptable in general.

13. Rejection and re-use of materials

Reprocessing and reworking

Reprocess and reworking were managed according to an SOP. The OOS material handling SOP covered reprocessing and rework of products. Regulatory approval was required before a batch was

reworked and a concurrent validation plan would been in place before a reworking took place. However, in general, reworking was not conducted..

Recovery of materials and solvents

Routinely, solvent was recovered from the mother liquor of manufacturing process. The specifications and recovery processes of recovered solvents were documented and found satisfactory.

14. Complaints and recalls

A complaint was made in 2014 and the relevant batches returned in June 2015. The investigation report was reviewed during the inspection. The investigation was performed and root caused identified. The CAPA included the requirement for operator retraining.

15. Contract manufacturers (including laboratories)

Contract manufacturing and contact testing were not applied to Mebendazole API.

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. Mebendazole API (APIMF 220) manufactured at Changzhou Yabang-QH Pharmachem Co. Ltd., located at Survey Number DUNS 527929456 Latitude 31.9744N Longtitude 119.9663E, 18 Jinlong Road, Chunjiang Town, Xinbei District, Changzhou, Jiangsu. P. R. China 213127was 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