

**Prequalification Team Inspection services  
WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
Finished Product Manufacturer**

| <b>Part 1</b>  | <b>General information</b>   |
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| <b>Manufacturers details</b>   |  |
| Company information  |  |
| Name of manufacturer   | <b>Questa Care Ltd.</b>  |
| Corporate address of manufacturer  |  |
| <b>Inspected site</b>  |  |
| Address of inspected manufacturing site if different from that given above | Plot No. 209/7184 Homabay Road Terminus,<br>Gate No. 19 Nairobi<br>Kenya   |
| Unit / block / workshop number   | NA   |
| Manufacturing license number, (delete if not applicable)                   | BU201500626 from Pharmacy and Poisons Board Kenya  |
| <b>Inspection details</b>  |  |
| Dates of inspection  | 15 to 17 August 2016   |
| Type of inspection   | Initial GMP inspection   |
| <b>Introduction</b>  |  |
| Brief summary of the manufacturing activities                              | Primary packing and secondary packaging of tablets<br>Quality Control testing (in-process quality control testing)<br>Importing<br>Batch release<br>Storage and distribution   |
| General information about the company and site                             | Questa Care Ltd. was established in 2012 and is located on Plot No. 209/7184 Homabay Road Terminus, Gate No. 19 Nairobi Kenya. The company is involved in primary packing and secondary packaging of oral solid dosage forms including tablets. There are no hormonal and cytotoxic products packaged on site. Questa Care Ltd. is a contract packaging site for Mylan Laboratories, Hyderabad India; the latter a WHO prequalified pharmaceutical manufacturing facility. |

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|---|--|
|   | <p>The site is surrounded by Nairobi flour mills on the southern side, empty go downs and a rail line on the northern side, supermarket on the eastern side and motorcycle sales and motor garage on the western side. There was no potential contamination from the surrounding industries listed above. The built-up area is 625m<sup>2</sup> on a plot area covering 0.2363 Ha. At the time of inspection the company employed 16 skilled workers of which 3 were in production, 5 in quality assurance, 2 in engineering and 2 in the warehouse. The 20 unskilled staff stated in the Site Master File were not on board because there was no commercial packaging going on.</p> <p>The packing line capacity is 8 million packs per annum on two shifts basis; with the first shift from 8am to 3pm while the second shift from 3pm to 11 pm.</p> |
| History   | This was the first WHO Prequalification (PQ) scheme inspection. The site was inspected and licensed by the local drug authority, Pharmacy and Poisons Board, Republic of Kenya.  |
| <b>Brief report of inspection activities undertaken</b> |  |
| <b>Scope and limitations</b>                            |  |
| Areas inspected   | The inspection focused on the primary packing, secondary packaging and control of the Lamivudine, Nevirapine and Zidovudine tablets 150mg/200mg/300 mg manufactures for PQ into 60's High Density Polyethylene (HDPE) bottles and other products listed under Part 1. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.   |
| Restrictions  | None   |
| Out of scope  | None   |
| WHO product numbers covered by the inspection           | <p>Products included in WHO Prequalification Programme:</p> <ul style="list-style-type: none"> <li>a) HA426 Lamivudine, Nevirapine and Zidovudine tablets 150mg/200mg/300mg</li> <li>b) HA433 Lamivudine/Nevirapine/Zidovudine Tablet, Dispersible 30mg/50mg/60mg</li> <li>c) HA456 Abacavir (sulfate)/Lamivudine Tablet, Film-coated 60mg/30mg</li> <li>d) HA466 Efavirenz/Lamivudine/Tenofovir Disoproxil (fumarate) Tablet, Film-coated 600mg/300mg/300mg</li> <li>e) HA393 Abacavir (sulfate) Tablet, Film-coated 300mg</li> <li>f) HA403 Efavirenz Tablet, Film-coated 600mg</li> <li>g) HA414 Lamivudine/Tenofovir Disoproxil (fumarate) Tablet, Film-coated 300mg/300mg</li> </ul>  |

|               |       |   |
|---------------|-------|---|
| 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 |  |

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|---------------|--|
| <b>Part 2</b> | <b>Brief summary of the findings and comments (where applicable)</b> |
|               |  |

### *Brief summary of the findings and comments*

#### **1. Pharmaceutical quality system**

The quality policy of Questa Care Ltd. entailed commitment to improve the quality of life in public health through provision of high quality pharmaceutical products and innovation to meet and exceed the needs and expectation of their customers. The specific laboratories where testing of the product was undertaken was not clearly stated in the Site Master File document reviewed prior to the inspection. It was stated that Vimta Laboratories India and MEDS Kenya were proposed.

There was a Quality Unit independent of production consisting of Quality Assurance, Regulatory Affairs, In-process Quality Control.

Responsibilities for key personnel were specified in job descriptions. There was a training program for new employees as well as refresher training activities on current and revised procedures.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

#### **2. Good manufacturing practices for pharmaceutical products**

In general good manufacturing practices were implemented. The necessary resources in terms of personnel, equipment and documentation were provided. Packing and packaging steps were recorded in batch packaging records. Instructions and procedures were generally written in clear and unambiguous language. Qualifications and validations were performed; adequate premises and equipment were available for packaging, in-process controls and storage. Operators were trained in the procedures and activities they had to perform. Procedures and record books were easily accessible, equipment were well maintained with appropriate status labels.

#### **3. Sanitation and hygiene**

The facilities and procedures for sanitation and hygiene established on the site were found to be adequate to ensure that premises and equipment were properly cleaned. All equipment inspected were in an appropriate condition.

The gowning and changing procedures for entry into the packaging facilities were satisfactory and adequately described in SOPs (illustrated) which were displayed on the wall. However, personnel accessed the primary packing area with partially open shoes.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

#### **4. Qualification and validation**

The Validation Master Plan document containing the guidance on the plan for validation of key processes and qualification of equipment was available and reviewed. Documentary evidence in form of qualification reports was available to show that the equipment had been designed, installed, operated in accordance with their design specifications.

#### **5. Complaints**

Complaints were handled according to SOP. Head, Quality Assurance was in charge of receiving, logging classification, investigation of complaints. The complaints were classified as Critical, Major and Minor. There was a clear distinction of complaints arising out of efficacy (adverse effects) and those out of quality defects.

The SOP for site interface with qualified persons, business partners and agencies explained the interface between Mylan and Questa. However there was no express indication of the responsibility of Questa. The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable.

The register for the complaints was available there were no entries as the site had not commenced with commercial packaging of the product.

#### **6. Product recalls**

The recall SOP was reviewed. There was no recall in 2015-2016 as commercial manufacturing had not commenced.

- The SOP did not mention notification to the regulatory Authority
- There was no link between Complaints and Recall SOP
- There was no classification of product recalls

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

#### **7. Contract production, analysis and other activities**

Quality control operations including stability testing was contracted out to MEDS Kenya and Vimta Laboratories, India. The calibration activities were contracted out. The contracts for the items discussed during inspection were in place.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

## **8. Self-inspection, quality audits and suppliers' audits and approval**

The SOP for internal Quality Audits was reviewed. The internal quality audit schedule was executed as per plan. The SOP does not expressly indicate who are the auditors, their qualification or experience. In section 6.2.2 of the procedure it was stated that the audit team shall comprise of auditors preferably from cross functional areas along the QA personnel.

The scheduled audit on the 18th March 2016 was carried out by one auditor, yet section 6.2.1 of the SOP indicated the audit team will be comprised of minimum two people. The audit for quality assurance department carried out on the 24th of March 2016 was carried out by one auditor who was part of the department.

Vendor qualification list and programme in accordance with procedure was reviewed. The company used questionnaires and on-site visits for printed packaging materials whereas only questionnaires were used for unprinted packaging materials. Suppliers of printed packaging material were first assessed using a questionnaire and then an on-site visit. Unprinted packaging material was assessed using a questionnaire. Two assessments for printed packing materials for vendors in Kenya were carried out.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

## **9. Personnel**

The organogram and job descriptions were in place. Individual responsibilities were defined and recorded as written job descriptions. The people met during inspection appeared competent and had a good understanding of GMP requirements. From the organogram the quality assurance manager and production manager were independent and they were both reporting to the director.

The job responsibilities for Production Manager and executive director operations were reviewed and found adequate. Personnel were considered competent with appropriate qualifications.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

## **10. Training**

Training was conducted using SOP. The procedure's effective date was 28th May 2016. It was found adequate in content and procedure. Training on GMP scheduled for 21st March 2016 was undertaken on the 7th of January 2016. Training records for the executive production officer were reviewed. The annual training calendar was not adequate in the sense of planning and execution of modular training. It was noted that GMP training and evaluation using a questionnaire consisting of 300 mixed questions was undertaken within 2 hours (3pm to 5pm). This raises the issue of adequacy and effectiveness of training.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

## **11. Personal hygiene**

The level of hygiene observed and the measures taken to maintain the facility were considered acceptable. Hand washing, washroom, and changing facilities were available in the first change room prior to accessing the manufacturing area.

Personnel changed from street clothing to factory clothing including head covers and factory shoes before accessing the manufacturing areas. Additional clothing was provided for personnel accessing areas where the product was exposed like the primary packing area and visual inspection area. Clear procedures for gowning including pictograms were displayed on the walls.

There was no provision for additional gowning prior to accessing the weighing area.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

## **12. Premises**

Buildings and facilities used for packaging and storage were located, designed, and constructed to facilitate proper cleaning, maintenance and packaging operations. Premises were designed to ensure the logical flow of materials and personnel. In-process laboratory was located in the packaging block. However it was small without proper ventilation. The wash up area space was not adequate to allow separation of dirty and clean equipment. The water treatment unit was located in the same area. Sufficient space was given to avoid mix-ups and cross-contamination for the packaging operation. Premises were protected from entry by insects, birds and rodents. Premises were clean and well maintained.

### Storage areas

The warehouse for the storage of bulk and packaging materials was found to be adequate. Temperature mapping was performed and found to be acceptable. Segregation was provided for the storage of rejected, recalled, or returned materials or products. Materials and products were protected from the weather however the canopy for the receiving bay was not large enough to adequately cover the materials on receipt

### Temperature and relative humidity mapping

The procedure for mapping of temperature and relative humidity effective date 30<sup>th</sup> May 2016 was reviewed. Temperature mapping protocol and report for bulk material store room for wet and dry respectively were reviewed. The mapping for both temperature and relative humidity was carried out for 7 days with recording at 5 minutes intervals. The calibration certificates for the Data loggers used during mapping were available for review. The mapping period was not indicative of the weather pattern in Kenya (April - October for the Dry season and November -March for wet season).



The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. The temperature mapping data will be verified in subsequent inspection.

At the time of inspection the company had acquired a new warehouse for packaging materials and finished goods store that was due for commissioning.

#### Packaging areas

The packaging area was laid out to allow the packaging steps to take place in a logical order. Surfaces were smooth and free from cracks. Equipment and materials were orderly positioned to minimize the risk of mix ups between the different status of packaged products and their components.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

### **13. Equipment**

Weighing balances were available for packaging and control operations and were calibrated on a scheduled basis following the verification and calibration procedure. Calibration due-date labels attached to the weighing balances were up to date. Annual calibration was undertaken by an external firm.

Packaging equipment was identified as to its content or purpose and cleanliness status using a label.

A qualification/calibration and preventive maintenance program for the year 2016 for all equipment on site was in place and was adequately followed.

### **14. Materials**

Materials were controlled by a manual system. The procedures for the receipt, identification, quarantine, storage, handling, sampling, approval or rejection of materials were inspected. Incoming bulk materials and packaging materials were quarantined after receipt until they were released for use. Materials and products were stored under the appropriate conditions. Temperature and Relative Humidity mapping studies were carried out.

Starting materials were obtained from the contract giver. Approved suppliers lists for starting materials (bulk tablets) and packaging materials were available. For each consignment, the containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material were recorded and reported to the QA department. Check-lists were used for materials receipt.

There were appropriate procedures in place to ensure the identity of the contents of each container of bulk materials. Bulk containers from which samples were drawn were identified.

### **15. Documentation**

The company had a master procedure for preparation, review, approval, distribution, revision, retrieval, archival and destruction of SOPs ref. no. The procedure for control of documents reference was reviewed.



The scope of the procedure for control of documents applied to system related documents issued by Quality Assurance at Questa yet there were other documents handled from contractors.

The procedure for Reprocessing and Reworking was reviewed. The company had a policy for not reprocessing batches on site. The rework order was to be approved by the Head QA.

The Master packaging record was reviewed during the inspection. The batch record for LNZ two batches were reviewed in accordance with the master record. The record reflected the performance of the different stages of the packaging operations. However, there were anomalies identified in the master record, recording of data and cleaning of the equipment.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

## **16. Good practices in production**

There was no production activity performed on this site. Only packaging processes were carried out. Measures to minimize risk of cross contamination and mix ups during packaging were implemented, this included status labels on machines and the rooms, log books were maintained, in process checks were done including leak test and weight checks.

There was logical flow of materials from visual inspection of tablets to primary filling line and eventually to the secondary packaging line.

Line clearance had been performed according to the procedure and recorded in the BPR. Bottle cleaning, filling sealing and labelling is an integrated process.

There was only one packaging line on site intended to be used for packing WHO products.

## **17. Good practices in quality control**

Quality control activities were contracted out to Mylan Laboratories. Questa performed only in process control tests and physical tests on the packaging materials. Sampling of bulk materials and packaging material was undertaken by the IPQC Personnel. Environmental control samples were taken by the contracted laboratory personnel from MEDS.

The in-process control laboratory was equipped with the leak test apparatus, pH meter, conductivity testing equipment and analytical balance. Standard operating procedures and usage log books for the equipment were available and found to be acceptable.

### **Microbiology laboratory and environmental monitoring**

Microbiology testing and environmental monitoring was contracted out to an external laboratory MEDS.

### **OOS**

The procedure for out of specification results and investigations was in place. There were no OOS results identified for the three batches processed.

### **Stability testing**

The stability study room was fitted with two stability study chambers for real time and accelerated stability testing at the following set temperatures and relative humidity:

a) Temperature  $40\pm 2^{\circ}\text{C}$ , RH  $75\pm 5\%$  b) Temperature  $30\pm 2^{\circ}\text{C}$ , RH  $75\pm 5\%$  The stability study chambers had been qualified and were found within the stipulated conditions; charging and withdraw of samples was appropriately recorded.

Stability testing programme was reviewed. It described the procedure for preparation, review, approval of stability protocol, collection of stability samples and carrying out of the stability program as per approved protocol. Questa Care Ltd. was responsible for charging samples in the chamber and Mylan for testing. Errors were observed in the record of the stability study testing report.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable.

### **Handling and storage of retention samples**

Seven packs per batch were picked and were retained for one year after the shelf life

Retention samples were stored at  $25^{\circ}\text{C}$  yet the product was labelled with storage conditions of “store below  $30^{\circ}\text{C}$ ”.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

## **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, *Questa Care Limited, Plot No. 209/7184 Homabay Road Terminus, Gate No. 19 Nairobi Kenya*, located at 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***

1. 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/](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.  
<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-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/](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](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](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](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](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](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](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](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](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/](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/](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](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](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](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](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](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  
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