World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

**Prequalification Team Inspection services**
**WHO PUBLIC INSPECTION**
**(WHOPIR)**
**of the FPP manufacturer**

| **Part 1** | **General information** |
|---|---|
| **Manufacturers details** | |
| Company information | |
| Name of manufacturer | Acme Formulation Pvt. Ltd. |
| Corporate address of manufacturer | Ropar Road Nalagarh Dist. Solan<br>Himachal Pradesh, 174101 India |
| Contact person | Mr. Viral Shah viralshah@acmeformulation.com |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | Ropar Road Nalagarh Dist. Solan<br>Himachal Pradesh, 174101 India |
| **Inspection details** | |
| Dates of inspection | 17-19 January 2018 |
| Type of inspection | Routine inspection |
| Representative from the National Regulatory Authority | Central Drugs Standard Control Organization (CDSCO) was invited and attended the inspection |
| **Introduction** | |
| Brief summary of the manufacturing activities | The site on Ropar Road consisted of two separate production blocks for the manufacture of solid dosages forms (tablets and capsules). The Hormones Block was inspected. Dedicated warehouses and chemical - microbiological laboratories were available for each block. |
| History | This was the second WHO inspection. The previous WHO inspection took place during 11th-14th August 2015. The site was also inspected by FMHACA Ethiopia, NDA Uganda and DPML Ivory Coast in 2016 and by MCAZ Zimbabwe, INVIMA Colombia and TFDA Tanzania in 2017. |
| **Brief report of inspection activities undertaken** | |
| **Scope and limitations** | |
| Areas inspected | **Document reviewed including but not limited**<br>• Quality Manual - Management Review<br>• Organization Chart<br>• Job descriptions for key personnel<br>• Product Quality Review |

| | |
|---|---|
| | • Quality Risk Management<br>• Responsibilities of the quality units and production<br>• Complaints and Recalls<br>• Deviation control and change control<br>• OOS and investigation<br>• CAPA procedure<br>• Material release<br>• Validation and qualification<br>• Equipment calibration<br>• Data integrity<br>• Sampling and testing of materials<br>• Batch processing records<br>• Materials management system<br>• Purified water system<br>• Heating, Ventilation and Air conditioning system<br>**Site visited:**<br>• Hormone Block<br>• QC laboratories including chemical and microbiological<br>• Starting material and finished goods warehouse |
| Restrictions | The focus of the inspection was storage, production quality control operations and areas where WHO prequalified products were manufactured |
| Out of scope | Products not submitted to WHO for Prequalification |
| WHO product numbers covered by the inspection | Dosage form inspected: tablets |

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 |
| | | MACO | Maximum Allowable Carry Over |
| | | 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** |
|---|---|

## 1. Pharmaceutical quality system

The company had a reasonably well documented pharmaceutical quality system (PQS) with Quality Manual, policies and written procedures covering essential GMP principles for the site. Quality assurance

(QA) function was involved and had oversight of all activities with impact to product quality. Quality Assurance was also responsible for batch release and a procedure was available. The Quality Manual was presented and was briefly reviewed during the inspection. Principles relating to data integrity, handling of complaints and returned goods/recalls were not described in the manual. Management review meetings were held periodically and the relevant procedure was made available during the inspection.

**Product quality review (PQR)**

A PQR procedure was in describing the steps to verify consistency of existing processes, appropriateness of established specifications for starting materials, in process and finished products as well as monitoring trends. A list of products for which PQRs had to be performed, was presented. PQRs had to be completed by 30th April every year. There was no provision for performing PQR for products that were not manufactured in the previous year and stability studies were not reviewed. Statistical analysis was carried out only if 6 or more batches were manufactured the previous year and control charts were only used to evaluate assay.

**Quality Risk Management (QRM)**

Quality Risk Management principles were generally applied to manufacturing operations and processes. FMEA was the tool of choice for performing risk assessments. Following the last WHO inspection observations the company had carried out a risk assessment on API suppliers and the protocol was presented. However risk assessments on excipients and packaging material suppliers were not presented. Fishbone diagrams were applied for root cause investigations and impact assessments.

**Change and deviation management**

Changes were managed according to a written procedure, describing in detail the steps to be taken, timeframes for implementation and personnel responsibilities. Changes were classified in two categories according to criticality but risk assessment was carried out after classification, only for major changes. Documentation was manually managed and archived. Review of open changes was performed on a monthly basis during management review meetings. A change of production equipment, addition of a new Multi-mill was reviewed. The company was in the process of implementing an electronic documentation system for the management of changes and deviations..

The procedure on “Handling Deviations Incidences” was reviewed. Root cause investigations were documented and where applicable Ishikawa diagrams were used. The final report was approved by Head QA. Although deviations were reviewed quarterly, recurrence was not always identified and as a result CAPA evaluation was incomplete.

**CAPA management**

CAPA were registered and managed manually and the ones relating to deviations were cross-referenced in deviation reports. However the same approach was not followed for CAPA relating to self-inspection. Quality Assurance department was responsible for reviewing CAPA implementation. Trending was performed at the end of the year. However the procedure did not describe in detail the parameters to be trended.

**Investigation of OOS**

The procedure for OOS results was reviewed. OOS investigations were performed in two phases. During the first phase the investigation was carried out by the analyst who reported the OOS result under the supervision of QA. In phase two a second analysis by a second analyst was carried out to verify the

results of the first analyst. Although the procedure covered the principles of OOS reporting, it required improvement in terms of providing appropriate instructions for root cause investigations and evaluation of OOS results.

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

Basic principles of good manufacturing practices were described in SOPs. Manufacturing processes were defined and reviewed. Three recently completed BMRs were reviewed. Manufacturing steps were recorded in Batch Manufacturing Documentation although some discrepancies in line clearance and packaging were identified. Manufacturing records were generally registered contemporaneously with relevant operations. Storage and distribution of products ensured batch traceability.

**3. Sanitation and hygiene**

Premises and equipment were generally cleaned according to established procedures. Nevertheless it was noted that cleaning materials were not always readily available and in close proximity to the areas requiring cleaning. It was also observed that there was no procedure in place for disposing cleaning materials that had come in contact with surfaces contaminated with hormones. Although two lipid-soluble APIs were used for the manufacture of finished products, in the sex hormone area, water was used for cleaning equipment and tools. Isopropyl alcohol 70% was used as a sanitization agent. The procedure and practices on operation and cleaning of the reverse laminar air flow hood in the sampling/dispensing area were checked. Similarly the procedure and practices on operation and cleaning of raw material sampling/dispensing/sieving/blending isolator were reviewed.

**4. Qualification and validation**

The key elements of the qualification and validation program were defined and documented in the Validation Master Plan. This was a standalone document containing details on all validation/qualification activities including but not limited to equipment, utilities, processes and cleaning, analytical methodology and computer systems. However there was no procedure in place providing instructions on planning, monitoring and documenting equipment re/qualification. Spot checks on equipment requalification were made and some discrepancies were identified. Also requalification of the HVAC system and the blending isolator were reviewed. Process validation was based upon the principles of process design, process qualification and continued process verification. Cleaning validation protocol and report were reviewed and CAPA relating to last WHO inspection findings were implemented. In order to determine the worst case scenario a risk assessment was carried out taking into consideration several parameters including solubility of API in water, difficulty in cleaning, complexity and design of equipment required in manufacturing.

**5. Complaints**

The company had in place a procedure on registering, investigating and monitoring complaints. The 2016 and 2017 complaints were spot-checked. It was noted that complaints were not reviewed periodically and therefore recurrence could not be easily identified. In general investigations were conducted and concluded within the appropriate timeframe and CAPA were identified and implemented

**6. Product recalls**

A procedure on product recall was presented. Head QA was responsible for coordinating recall activities. Recalls were categorized in three classes according to criticality and notification urgency. The most recent mock recall was carried out in April 2017. There was also a procedure in place on handling

returned goods which was linked to the recall procedure and provided instructions on managing returned products to the warehouse.

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

A third party was contracted for performing certain HPLC, IR and GC analyses of raw materials and finished products. A contract between the two companies was established. A logbook for registering outgoing samples was available. Acme monitored the timeframe for completion of outsourced tests and dates were recorded in the logbook. Analyses and relevant certificates originating from the contractor were checked and signed upon receipt at Acme.

Housekeeping and cleaning was also contracted to a third party. The contractor provided both supervisors and workers to Acme. A contract between the companies was available. Acme was responsible for medical clearance of contract personnel and providing appropriate training. Records for training and medical examinations were presented.

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

A procedure on self-inspection was available. Self-inspections were carried out quarterly by qualified auditors according to a written procedure. A report with observations was compiled but it was not defined how CAPA related to audit findings were documented and followed up.

A system for vendor qualification was in place. A risk assessment on API suppliers was performed in 2015 but no risk assessment was carried out for excipient and packaging materials suppliers. Spot checks were performed on excipient suppliers and packaging material suppliers. It is recommended that the company improves supervision of its suppliers.

**9. Personnel**

Functional and hierarchical organization charts were presented. There was an SOP on job responsibilities. QA was responsible for batch release and monitoring of stability studies. Job descriptions of Production Manager, Warehouse Manager, QC and QA Managers were requested for review and they were made available. Acme contracted personnel for housekeeping and there was a procedure available, providing sufficient instruction on handling contract personnel.

**10. Training**

Training was performed in accordance with an internal procedure and it was carried out based on an annual program which was compiled based on identified training needs. A separate procedure on induction training was also available, describing introductory GMP training to newly recruited personnel. The 2017 training programme was reviewed and spot checks on training records of contract personnel were made.

**11. Personal hygiene**

General principles of hygiene ware applied. Instructions and pictorials to be followed were sufficiently clear when it came to personal hygiene. Personnel gowning procedure was appropriate and was generally followed. A procedure on medical examinations was in place. For new personnel including contract personnel, medical examinations were foreseen before joining the company and yearly afterwards. Sensitivity and thyroid tests were included in the list of medical examinations.

**12. Premises**

Storage areas for warehousing of raw materials and finished products were of sufficient capacity and were located on the ground floor. Temperature was monitored and recorded manually, three times a day and the temperature logger was installed at the hottest point which was identified during the temperature mapping exercise. However relative humidity was not monitored in the warehouse. A refrigerator was available for storage of temperature sensitive materials. Sampling and dispensing of excipients took place in the same suite, located adjacent to the warehouse. Production areas were located on the 1st floor and they were appropriately designed and maintained. The production corridor was over-pressured compared to production rooms and personnel dressing rooms. The same entrance to production areas was used for personnel and visitors and access control was established. The chemical and microbiological laboratories were located on separate floors. It was noted that space in the microbiological laboratory was limited. The company had already identified this issue and was looking into constructing new laboratories.

## 13. Equipment

Manufacturing equipment was appropriately installed. Scales were verified daily according to an established procedure. Rigid isolators were installed for high risk operations (e.g. sampling, dispensing, sieving, blending). Low risk operations (e.g. primary packaging) were carried out under flexible isolators or in combination with portable respirators. Sampling/Dispensing/Sieving/Blending Isolator was installed in one production room. This isolator recirculated air from the room through HEPA filters and established negative differential pressure compared to the room. An equipment maintenance program was presented.

Six AHUs were installed in the hormone block with maintenance carried out according to procedures.
A Purified Water generation and distribution system with 13 user points was installed. Purified Water was generated from soft water by ultrafiltration followed by reverse osmosis and deionization treatment and it was collected in a SS316L storage tank. The validation plan was divided in three phases where the 1st phase was 4 weeks, the 2nd phase was 4 weeks and the 3rd monitoring phase lasted 1 year. The qualification report of phase 3 was reviewed. Trending was performed and all user points were monitored according to relevant procedures (SOP/HQ/043/03 for chemical, SOP/HQ/039/03 for microbial).
The 2017 trend analysis report was reviewed, but no document reference number was assigned to it.

## 14. Materials

There was a procedure in place describing receipt and storage of raw materials. A check list was used for receipt. Quarantine labels were issued by an ERP system operated by warehouse personnel. A sampling/dispensing room for excipients was adjacent to the warehouse. Separate entries for personnel and excipients were available in the sampling room. Operation and cleaning of the sampling/dispensing booth was performed according to an established procedure

## 15. Documentation

In general, the documentation system was satisfactorily established and maintained; documents were approved, signed and dated by QA, reviewed and kept up to date. Documentation was categorized in 3 classes according to criticality and applicability. Procedures were amended through change control. A list of procedures was available. In certain occasions it was observed that a versioning system was not applied in all GMP documentation. Specifications and testing procedures were available.

## 16. Good practices in production

Production areas in the Hormone Block were visited. The same entrance was used for personnel and visitors and pictograms provided basic instructions for gowning. The facility was normally operating

with two shifts per day. At the time of inspection, production operations were ongoing. Areas inspected included sampling/dispensing/sieving/granulation room, compression rooms and packaging areas. Line clearance was documented on the batch records. Checks on yields and reconciliation of raw material quantities were carried out. Rooms, equipment and materials were appropriately labelled. Punches and dies were product dedicated and rotation was documented. Dispensing, sieving and blending of bulk product was carried out in an isolator in the sex hormone suite. Following compression bulk tablets were taken to primary packaging area where the packaging line was under a flexible isolator. Operator interventions were made through glove ports or by unzipping appropriately designed windows on the flexible isolator. BMRs and BPRs were spot checked as well as maintenance and calibration of equipment.

**17. Good practices in quality control**

Chemical and microbiological laboratories were located on different floors. There were separate rooms for instruments for chemical analysis. Following last WHO inspection observations, the company had established a procedure on data management and data integrity in Quality Control. However further improvement is expected because discrepancies on the application of this procedure were identified. Relevant procedures on technology transfer and computer system backup and restore were reviewed.

A separate entrance was used for the Microbiological laboratory. The premises included the preparation area and the testing area. However it was noted that the laboratory was quite small and there was not sufficient space. Records for performance of microbiological testing were reviewed and traceability was appropriate and adequately documented. Culture media were prepared according to relevant SOP and a procedure on growth promotion was presented. Standard microorganisms for testing were stored and used according the written procedures

**PART 3 - Conclusion**

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as the Corrective Actions taken and planned, ***Acme Formulation Pvt. Ltd. Ropar Road Nalagarh Dist. Solan, Himachal Pradesh, 174101 India,*** was considered to be operating at an acceptable level for compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full inspection report as well as those reflected in the WHO Public Inspection Report (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- References**

***List of GMP guidelines used for assessing compliance***

1. WHO good manufacturing practices for sterile pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
***Short name: WHO TRS No. 961, Annex 6***

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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/
***Short name: WHO TRS No. 986, Annex 2***

3. WHO good manufacturing practices for active pharmaceutical ingredients. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report* Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
***Short name: WHO TRS No. 957, Annex 2***
http://www.who.int/medicines/publications/44threport/en/

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

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

6. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
***Short name: WHO TRS No. 961, Annex 5***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

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

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

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

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

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

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

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

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

16. WHO guidelines for drafting a site master file. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14

***Short name: WHO TRS No. 961, Annex 14***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
***Short name: WHO TRS No. 992, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
***Short name: WHO TRS No. 992, Annex 4***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
***Short name: WHO TRS No. 992, Annex 5***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
***Short name: WHO TRS No. 992, Annex 6***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
***Short name: WHO TRS No. 996, Annex 3***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
***Short name: WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
***Short name: WHO TRS No. 996, Annex 10***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf