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

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Company information | |
| Name of manufacturer | Zhejiang Huahai Pharmaceutical Co., Ltd |
| Corporate address of manufacturer | Xunqiao, Linhai, Zhejiang Province, 317024, China |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | Xunqiao, Linhai, Zhejiang Province, 317024, China |
| Unit / block / workshop number | Building F1: Workshop I |
| Manufacturing license number, (delete if not applicable) | ZE20000311 |
| **Inspection details** | |
| Dates of inspection | 25 – 28 July 2017 |
| Type of inspection | Initial inspection (New site) |
| **Introduction** | |
| Brief summary of the manufacturing activities | Production and Quality Control of API and oral solid dosage forms |
| General information about the company and site | Zhejiang Huahai Pharmaceutical Co., Ltd is located in Xunqiao Town, Linhai City, Zhejiang Province, P.R. of China. The Finished Dosage Form (FDF) Building F1 was located east of the company premises and was built in 2001; it houses formulation workshop I, II, III, IV, VI and warehouse I. Approximately 1600 people are employed at the site at the time of inspection.<br><br>The two products, within the inspection scope, namely Efavirenz and Raltegravir film coated tablets, were manufactured in Workshop I in Building F1. Zhejiang |

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| | Huahai Pharmaceutical Co., Ltd performed contract manufacturing of these two products for product prequalification holder Merck Sharp & Dohme Interpharma and Merck Sharp Dohme BV respectively. It was a non-dedicated workshop with different products manufactured. |
| History | This was the 1st WHO inspection. The site was inspected by the USFDA (June 2017) and the Regulatory Authority of Hamburg, Germany (BGV) (April 2017). The site was regularly inspected by the CFDA (July 2017). |
| **Brief report of inspection activities undertaken** | |
| **Scope and limitations** | |
| Areas inspected | • Starting Material, Packaging Components, Product Intermediates and Finished Product Warehouses, including sampling areas<br>• Production facilities in Building F1, Workshop I<br>• QC facilities including Analytical Chemistry and Microbiology Laboratories in Building C1 and C2, respectively<br>• Systems for Purified Water<br>• HVAC Systems<br>• Documentation, including SOPs, Batch Manufacturing Records (BMRs) etc. |
| Restrictions | Nil |
| Out of scope | Finished Products not submitted to WHO for Prequalification |
| WHO product numbers covered by the inspection | Efavirenz film coated tablet 600 mg (HA337)<br>Raltegravir film coated tablet 400 mg (HA673) |

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 |

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|---|---|
| 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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**PART 2**
***Brief summary of the findings and comments***

## 1. Pharmaceutical quality system

The system for quality assurance (QA) was satisfactorily controlled through the application of key quality principles.The review of the quality management system (QMS) and related QA procedures demonstrated that for example:

- Production and quality control operations were generally specified in approved documentation;
- The necessary procedures were generally in place to ensure the use of correct starting and packaging materials;
- Internal audits were performed on a regular basis to ensure compliance with, and appropriateness of, the QMS;
- The quality risk management (QRM) system was generally satisfactory and ensured that, where relevant, a risk assessment, commensurate with the level of risk, was performed; and
- The annual product quality review was generally satisfactory in that it provided documented assurance of the ability to consistently produce products which met the appropriate specifications.

**Product quality review**
An annual product quality review management procedure covered the product annual review process. At the time of the inspection, the product quality review, of the two products in the inspection scope, for the year 2016, had not yet been completed according to the company PQR annual plan.

The 2015 PQR for Efavirenz 600 mg film coated tablets was reviewed. The product had two different codes, CP for Chinese market, ROW for rest of world. There was no product return and recall. There were two complaints. Non-compliances observed during the inspection that was listed in the full report regarding PQR were addressed by the manufacturer to a satisfactory level.

**Quality risk management**
An SOP for Quality Risk Management was available for inspection. A Quality Risk Management (QRM) process was generally followed, with product Risk Assessments documented. A risk assessment, commensurate with the level of risk, was performed for GMP related activities and in the event that a change control was initiated. A multi-faceted team, including representatives for Production, Quality Control, Quality Assurance (QA), Engineering and Technology, was responsible for performing risk assessments and the QA Department was ultimately responsible for approval. The procedure for quality risk management, including risk assessment, risk control, risk communication and risk review was generally satisfactory.

**Change and deviation management**

A deviation investigation management system described that in the event of a deviation, a root cause investigation and the relevant risk assessment would be performed. Deviations were classified as major or minor and planned deviations were managed according to a change control procedure. Investigations into reported deviations were performed by a multidisciplinary team and the QA Department took overall responsibility for the deviation procedure. The deviation system management included both monthly and annual review. A product deviation list for the period of the first half of 2017 was reviewed and deviations were generally observed to be handled satisfactorily.

A procedure for change control system was available. Change control requests were evaluated by a cross-functional change control committee and the impact of the change on regulatory, quality, technology, production, validation, documentation, etc. was considered. The QA department was ultimately responsible for the approval of change control requests and change management was generally satisfactory.

## 2. Good manufacturing practices for pharmaceutical products

Provision was made for the general implementation of, and compliance with, Good Manufacturing Practices (GMP). Resource commitment, in terms of personnel, facilities, equipment and systems was evident. Processes relating to production, qualification and validation were well defined and records thereof were available. Product was released by the authorized persons. The final product release of the two products within the inspection scope was performed by MSD.

## 3. Sanitation and hygiene

Premises and equipment were maintained at a satisfactory level of cleanliness. The company had a standard operating procedure in place to describe the basis for its approach to personal hygiene and sanitation in its production facility; with appropriate hand washing required. Clean areas were cleaned frequently in accordance with an approved written programme.

Personnel were seen to be performing their duties in a generally organized and diligent manner. Procedures were in place for the preparation and control of sanitizing materials used in the production areas.

## 4. Qualification and validation

Qualification and validation protocols were detailed and generally satisfactory. Reports were reviewed for PQ for a granulator and IQ/OQ for a tablet press machine. No deviations or change controls were recorded in the reports; critical process parameters were identified and the equipment was qualified through the upper and lower limits of the operating range.

A Qualification and validation procedure was available and considered acceptable. Process validation of Efavirenz tablet via change control was reviewed as well as the cleaning validation for Efavirenz and Raltegravir tablets. Non-compliances observed during the inspection regarding process validation were addressed by the manufacturer to a satisfactory level.

Computerised system (CS) was used in warehouse 2 and the QC laboratory. LIMS was installed last year and the qualification was ongoing at the time of inspection.

## 5. Complaints

Complaints were handled according to a documented procedure. Complaint Management Procedure, and were classified as serious or other, depending on the nature of the complaint. QA was responsible for the overall handling of the Complaint Management Procedure which was reviewed. The procedure identified that the investigation into the product complaint would be performed according to the deviation management procedure. The complaint management procedure made provision for the initiation of CAPA and where necessary, product recall.

A customer complaint list and a complaint regarding Efavirenz 600mg tablet were reviewed. Non-compliances observed during the inspection regarding complaint handling were addressed by the manufacturer to a satisfactory level.

## 6. Product recalls

A product recall procedure was available and was found to be generally satisfactory. There had been no recalls for the past several years for any of the finished pharmaceutical products (FPP) manufactured at this site. Recalls were classified as three grades, Grade 1 being the most serious. A mock recall was required to be performed on an annual basis and the protocol and report for the last mock recall appeared to be satisfactory.

## 7. Contract production, analysis and other activities

The products in the inspection scope, Efavirenz and Raltegravir tablets were manufactured on behalf of Merck and Co., Inc.(MSD), who were the PQ product application holder. The technical agreement between Huahai Pharmaceutical and MSD was reviewed and considered acceptable. Non-compliances observed during the inspection regarding implementation of the technical agreement were addressed by the manufacturer to a satisfactory level.

Two Quality Control (QC) Laboratories were sub-contracted to perform impurity testing of two of the excipients used in the production of Raltegravir 400 mg film coated tablets. Both of the contracted laboratories were located in the United States of America.

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

A self-inspection management procedure, indicated that self-inspections were performed every three months by authorised internal auditors, independent of the department inspected. A self-inspection plan for 2017 indicated that the most recent inspection was performed in June 2017 and an inspection report was available. CAPA progress and efficacy was managed by QA.

A documented system for supplier approval was in place and a management system of formulation material supplier was available. A formal supplier evaluation was conducted for new suppliers and onsite inspection was performed. The authorised list of approved suppliers and a schedule for vendor audit for 2017 were available. The general templates used for evaluation and management of new and existing suppliers were generally satisfactory. MSD, the contract giver for the production of the Raltegravir 400 mg and Efavirenz 600 mg film-coated tablets was responsible for supplier audit.

## 9. Personnel

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Personnel interviewed during the inspection were aware of the principles of GMP in general.
An organization chart was available and considered acceptable. Responsibilities of staff and their specific duties were recorded in written job descriptions and were reviewed.

## 10. Training

Training was managed according to a corporate training system procedure. The training plan for 2017 and the QC analyst qualification programme were reviewed. Weakness observed during the inspection that was listed in the full report regarding analyst qualifications were addressed by the manufacturer to a satisfactory level.

## 11. Personal hygiene

Smoking, eating, drinking and chewing was prohibited in production, laboratory and storage areas.

No concerns of note were identified during the inspection. The approach to sanitation and hygiene was in general acceptable.

## 12. Premises

Manufacturing areas were generally of a good standard and suitable for the operations to be carried out.
Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning agents and disinfectants where used.

Access to production areas was restricted. Two warehouses which were located in two different buildings were used to store raw materials, excipients, FDF and packaging materials. Separate receiving and dispatch bays were available. Storage areas were of sufficient capacity and goods that were quarantined, rejected and returned were adequately segregated.

QC laboratories were separated from production areas. Incoming samples were stored appropriately in an access-controlled cupboard and/or refrigerator and adequate storage space was provided for reference standards, solvents, reagents and related documentation.

The areas including warehouse, workshop 1 and QC laboratories used for production and quality control were inspected and considered to be acceptable and suitable for this type of production activity in general.

**13. Equipment**

The equipment installed was of a high standard and was well designed and appeared to operate effectively.

The IQ, OQ and PQ were available for one granulator and a tablet press. No deviations or change controls were observed during the reviewed qualification studies. Equipment qualification was documented in detail; critical process parameters were appropriately identified and qualification activities encompassed upper and lower operating limits.

Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Production equipment was cleaned on a scheduled basis.

A purified water system was inspected. The PW generation system connected to three distribution systems. Non-compliances observed during the inspection that was listed in the full report regarding the PW system were addressed by the manufacturer to a satisfactory level.

Operating and monitoring procedure on HVAC system SOP and AHUs for bottle filling area & for corridor in workshop 1 were reviewed and found generally acceptable.

**14. Materials**

Incoming materials and finished products were quarantined after receipt until they were released for use or distribution. The release procedure for Efavirenz and Raltegravir Potassium APIs were reviewed. Non-compliances observed during the inspection regarding release of Efavirenz and Raltegravir Potassium APIs were addressed by the manufacturer to a satisfactory level.

Materials in Warehouse I were managed through a manual system which controlled product bin location and product status. Materials were held under quarantine and labelled with a yellow label, until approval was obtained. Upon approval, quarantined materials would be labelled with a green label to indicate approval for release/use.

Materials in Warehouse II were managed in a computerized system. Management regulation on code of raw material, packaging material and finished product SOP was available for review.

Rejected goods were labelled as such and securely stored in a segregated area. Printed packaging materials were securely stored.

Reprocessing and reworking procedures were described in an SOP and appeared acceptable.

Waste material treatment warehouse was visited. Log books were available and appeared acceptable.

## 15. Documentation

Documentation was designed, prepared, reviewed and distributed according to an SOP. The QA department was responsible for the version control and review of all documentation and a current index of SOPs were available.

Specifications, manufacturing formulations and instructions, procedures, and records were up-to-date, authorised and generally satisfactory.

Paper-based batch manufacturing records (BMRs) and batch packaging records (BPRs) provided detailed processing instructions and made provision for recording of processing locations used, principal equipment used, batch traceability and batch yield.

BMRs and BPRs were retained for each batch processed. Line clearance and equipment status was confirmed and recorded before processing began.

BMRs and BPRs of Efavirenz, with a batch number were reviewed and observed to be generally satisfactory.

## 16. Good practices in production

Building F1 consisted of four workshops. Workshop I was used for the manufacture of tablets and capsules and packed into plastic securitainers. During the time of the inspection, no encapsulation equipment was observed in Workshop I. Both Efavirenz and Raltegravir film-coated tablets were produced in Workshop I. The production area in Workshop 1 was classified as Grade D and the corridors within the production area were maintained at a higher pressure thus facilitating containment of powder within processing cubicles.

The production of Efavirenz tablets for domestic market was in operation at the time of inspection. Packaging activities for Efavirenz tablets, were limited to primary packaging only.

Primary and secondary packaging of Raltegravir tablets was performed on site.

## 17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that the QC arrangements were effectively and reliably carried out. QC laboratories, including the microbiological laboratory, were separated from production areas.

The QC Laboratory was inspected. The personnel, premises, and equipment in the laboratory were appropriate to the tasks imposed by the nature and the scale of the manufacturing operations.

The receipt, sampling, testing and release of Efavirenz 600 mg film-coated tablets was reviewed as an example of material control. The results of the analysis were traceable to reference substances, equipment and instruments used for analysis. The QC procedures, test methods and records were generally satisfactory.

Appropriate storage of reference standards, retention samples and HPLC columns was noted. Reagents and volumetric solutions prepared in the laboratory were appropriately labelled and Grade "A" volumetric glassware was used for analysis.

Emergency showers and eye wash equipment were provided.

Microbiological Laboratory

The Microbiology Laboratory was separated from the Chemistry Laboratory. Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. Media preparation procedure, record, PW testing procedure, sample receiving and distribution, testing results monitoring were all reviewed and found generally acceptable.

OOS

SOP on Lab OOS/OOT investigation management procedure was reviewed and OOS log book was available. They were generally observed to be acceptable.

Stability Testing

A written programme for stability study was available. Stability and on-going stability study for these two products were tested by MSD with the batch sample selected by Huahai Pharmaceutical.

## 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, **Zhejiang Huahai Pharmaceutical Co., Ltd located at Xunqiao, Linhai, Zhejiang Province, 317024, China** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

**PART 4**

***List of GMP guidelines referenced in the inspection***

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   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-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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