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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Liaoyuan Silver Eagle Pharmaceutical Co., Ltd.
Corporate address of manufacturer	No. 2 Wealth Northern Road, Youyi Industry Area of Liaoyuan Economic Development Zone Liaoyuan, Jilin Province, 136200 China
Inspected site	
Name & address of inspected manufacturing site if different from that given above	No. 2 Wealth Northern Road, Youyi Industry Area of Liaoyuan Economic Development Zone Liaoyuan, Jilin Province, 136200 China
Synthetic unit /Block/ Workshop	WS No.3
Inspection details	
Dates of inspection	08 to 11 July 2019
Type of inspection	Follow-up inspection
Introduction	
Brief description of the manufacturing activities	Manufacturing and quality control of APIs and intermediates.
General information about the company and site	Liaoyuan Silver Eagle Pharmaceutical Co., Ltd. (hereinafter referred to as Silver Eagle) is a privately-owned company established in 1978. There were 163 employees in total at the time of inspection. A Chinese manufacturing license included API products list was in place. Some APIs were registered with CFDA and held Chinese GMP certificates. Currently the company does not hold a domestic Chinese approval for para-amino salicylate monosodium hydrate (PAS) API. The site is in an industrial area of Liaoyuan. There were no penicillin and other β-lactam products, cytotoxics or other high potent materials manufactured on this site.

History	This was the third WHO inspection of the site. The previous inspections were conducted in June 2018 and April 2017. The company held a CEP of a different API but has not been inspected by any European agency yet. The site was inspected by USFDA in 2011 for different API products.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	This was a follow up inspection to the WHO inspection performed in June 2018 and focused on the issues arising from the previous inspection as well as the production and control of para-aminosalicylate monosodium dihydrate in WS No.3. The inspection covered the CAPAs implemented following the major deficiencies observed in the previous inspection as well as most of the sections of the WHO GMP text including, • Quality management • Personnel • Buildings and facilities • Process equipment • Documentation and records • Materials management • Production and in-process controls • Packaging and identification labelling of APIs and intermediates • Storage and distribution • Laboratory controls • Validation • Change control • Rejection and reuse of materials • Complaints and recalls • Contract manufacturers (including laboratories) **Areas visited:** • WS No.3 • QC laboratories • Warehouses • Purified water system
Restrictions	Other processes and/or grades of PAS API products outside of WHO pre-qualification were not inspected during this inspection.
Out of scope	API products other than Para-aminosalicylate monosodium dehydrate (APIMF307) manufactured on this site were outside the scope of this inspection.

WHO APIs covered by the inspection	Para-aminosalicylate monosodium dihydrate (APIMF307)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control

QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RH	Relative humidity
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

Part 2	**Summary of the findings and comments**

1. Quality management

A general system for quality assurance was established, with procedures covering key quality elements being in place. Operations were specified in a written form and GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of an acceptable standard. Product and processes were monitored, and these results considered during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

A company organogram is available. The Quality Unit was divided into QA and QC. The Unit was separate from the production department.

Product quality review (PQR)

PQR was performed according to an SOP. Several quality grades of PAS API were manufactured on site, i.e. WHO grade, BP Grade and as per customer requirement.

The PQR 2018 PAS Sodium for the period January to December 2018 was reviewed. The PQR included the results of all batches produced in the year. The CPP and CQA results were presented in a table and graphed. Trending was visible on the graphical data representations. There were no complaints, return and recalls in 2018. Deviation, OOS and CAPAs were reviewed in the PQR.

Deviations

Deviations were managed according to an SOP. Deviations were classified into critical, major and minor. The several deviations were reviewed during inspection. Non-compliances observed during the inspection that was listed in the full report regarding deviation management were addressed by the manufacturer to a satisfactory level.

CAPAs

CAPA was managed according to an SOP. The CAPA log books were maintained. Several CAPAs to the major deficiencies made in last inspection were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding the data management and computerized system were addressed by the manufacturer to a satisfactory level.

Self-inspection

GMP self-inspection management procedure was available. Internal audit is performed annually for all GMP activities. The deficiencies were rated as critical, major or minor. This was not reviewed in detail during the inspection.

2. Personnel

An organization chart was available. Since the last inspection there has been changes in personal in key positions, i.e. the QA and QC Managers. Key personnel responsibilities were specified in job descriptions. The job descriptions of the QP, managers of QA, QC and production were reviewed and found acceptable.

Training

The training of operator based on a CAPA was checked and found acceptable. The personnel met during the inspection appeared to have an acceptable knowledge of the principles of GMP and showed that they received training relevant to their respective responsibilities.

Personnel hygiene

Personnel were required to wear protective clothing suitable for the type and stage of manufacturing. Suitable sanitation and change room facilities were provided. Smoking and eating were not permitted in manufacturing areas.

3. Buildings and facilities

Design and construction

There were several production workshops (WS) on site. The WS No.3 was dedicated to the production of PAS API. The WS No.3 included chemical synthesis areas and a Grade D clean area to the final purification, drying and packaging of the API. The buildings and facilities inspected in WS No 3 were designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture.

Gowning procedures for staff and visitors appeared acceptable. Pictorials and charts were presented in the gowning areas before entering the Grade D area. Environmental control with temperature and humidity was monitored and recorded for all areas.

Utilities

HVAC

A dedicated HVAC system provided filtered air to WS No 3 Grade D clean area for final purification, drying and packaging of PAS API. The pressure differential magnehelic gauges were installed in appropriate areas in the clean room.

Water

Purified water was used in the final stage of PAS API manufacturing. Purified water system was located in Workshop No.3. The system was using double reverse osmosis to produce purified water. The system was regularly sanitized. The critical points in the PW distribution system was sampled and tested weekly. The rest using points were tested monthly.

Compressed air

Compressed air was in direct contact with the product during manufacturing. The OQ and PQ of compressed air were performed annually. It was not checked in detail in this inspection.

4. Process equipment

Design and construction

The process equipment used in WS No.3 was dedicated for the manufacturing of PAS. Design and construction were in general of appropriate for its intended use. Closed systems were used for most processes for manufacturing procedure when possible.

Equipment maintenance

Equipment was appropriately labeled with identification number and status. Preventive maintenance procedures and annual maintenance plans were available. The following documents were reviewed and found acceptable.

- Equipment maintenance plan and schedule for 2019
- WS No.3 maintenance Plan and schedule
- Maintenance plan and scheduled of a reactor
- Maintenance record of a reactor

Equipment cleaning

Equipment was required to be cleaned according to documented procedures. All the equipment located in WS No 3 were cleaned with purified water and checked visually. The equipment cleaning status was maintained at a satisfactory level in general. Cleaning procedure for some equipment was reviewed. Non-compliances observed during the inspection that was listed in the full report regarding equipment cleaning were addressed by the manufacturer to a satisfactory level.

Calibration

Calibration was performed according to company procedure and schedules. An operator demonstrated the weight check procedure on a balance in primary packing area and appeared acceptable.

Calibration record of a pH meter used for in-process control in WS No.3 was reviewed and discussed during the inspection.

Computerized systems

Computerized systems were not used for material or production control.

QC testing instruments were all standalone system at the time of the inspection. A computerized system used for data backup was introduce since last inspection; however, weakness was noted in this inspection. A new software has been introduced to networking of testing instruments and data being saved on servers after the inspection. Non-compliances observed during the inspection that was listed in the full report regarding the computerized system were addressed by the manufacturer to a satisfactory level.

5. Documentation and records

The documentation system was paper-based, and Excel were used for some records. The documentation was managed according to an SOP. Revision period of the SOPs was specified and implemented. QA approves all GMP related documents.

Batch Manufacturing Records

BMRs for WHO grade PAS API was reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding BMR were addressed by the manufacturer to a satisfactory level.

Batch testing Records

WHO batch testing followed a documented standard testing procedure. Analytic records of the API, HPLC chromatogram of starting material and intermediate testing were reviewed and discussed.

6. Materials management

A manual system was in place for handling raw materials, packaging material and finished products. There were written procedures describing the receipt, labelling, quarantine, storage, and handling of materials, as well as sampling, testing and approval or rejection of materials. Materials used for R&D purpose were stored in a separate room.

Material suppliers were required to be approved according to a supplier qualification procedure and audit. Material was classified into three categories. Key material suppliers were required on site audit periodically. The suppliers' audit was not reviewed in this inspection because the time constrains.

7. Production and in-process controls

Production operations

Production of PAS API was conducted in the dedicated WS No 3. The production in the chemical and grade D areas were in operation at the time of inspection. The manufacturing flow was in line with BMR for PAS process. Several points including process equipment, material charging, and process parameters monitoring were checked and found acceptable.

In-process controls

Sampling for IPC was conducted at defined stages during processing. QC was responsible to perform the IPC testing in QC laboratory.

PH testing to monitor process parameters was performed by production staff in the chemical synthesis area of WS No3.

Blending batches of intermediates or APIs
Blending operation was not applicable to the WHO grade PAS batches.

Holding time study
Holding time study for PAS API was spot checked. A holding time for the API after milling has been established.

Contamination control
Contamination was limited in view of the dedicated facility and equipment used for production of PAS API.

8. Packaging and identification labelling of APIs and intermediates

Packaging and labelling were not in operation during the inspection. PAS batch packaging records of WHO grade PV batches were available and reviewed. No deficiency was noted.

9. Storage and distribution

The warehouse for raw materials and APIs were inspected. Temperature and humidity requirements for finished PAS API warehouse were specified and were recorded. The results of regular monitoring were satisfactory. Temperature mapping in final product warehouse had been performed as required following implementation of CAPA as required by the previous WHO inspection.

Distribution procedures
APIs were released for distribution following approval by QA department according to a product release procedure. The WHO grade PAS API PV batches have not been approved for distribution to commercial market.

10. Laboratory controls

The QC laboratories were responsible for physical, chemical and microbiological testing of starting materials, packaging materials, API products, environmental monitoring samples and purified water samples. The following aspects in QC laboratory were inspected.

Sample receiving
No samples stored during the time inspection in the area. Record of samples received was available and checked.
Procedures for sampling process management and sampling of raw material were reviewed and found acceptable.

Testing of intermediates and APIs

Finished API specifications were available for all different grades of PAS APIs. Specification for WHO grade PAS API and testing procedure was checked. No comments were made.

No activity was performed in the balance room at the time of inspection. A balance was reviewed for labelling and maintenance schedule. Weights used for calibration was checked. Daily weight checked was performed. Balance management was conducted regularly.

Stability study of API

Stability study for WHO PAS API was performed at the condition 30ºC, RH75% for long term and 40^0C, RH75% for accelerated stability studies. Stability study for the three PV batches was performed. The report was reviewed and found acceptable.

A stability chamber alarm was checked for alarm activation. The alarm was functional. The chamber contained sealed bags with stability study samples of PAS API. A power failure back-up generator was installed.

Retention samples

Retention samples were kept in a secured and temperature-controlled area for PAS API products. A log book was in place. The packaging simulated the commercial product packaging.

Reference standards

Reference standard substances were kept in a secured and locked fridge. PAS reference substance was checked. The review indicted that primary RS and work reference standard were available and documented.

Handling of OOS/ OOT results

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

HPLC system review

Some HPLCs have been procured and installed since last inspection. Qualification/calibration of a HPLC was checked. No observations were made.
Columns were stored in a lock cabinet. Columns were not dedicated for specific APIs or related impurities.

Data management in computerized system

CAPAs to the identified deficiencies of the data management observed in the last WHO inspection in 2018 was reviewed. The following documents were reviewed,

- CAPA to computerized system and data integrity
- Validation protocol on computerized systems
- Procedure on laboratory electronic data security
- Data integrity and traceability of a PAS API testing sequence.

Some deficiencies were note. Non-compliances observed during the inspection that was listed in the full report regarding data integrity and electronic data review were addressed by the manufacturer to a satisfactory level.

Microbiological laboratory

The microbiology laboratory was briefly inspected. The media preparation and sterilization procedures, PW microbiological limit testing procedure and trend analysis of PW microbiological testing results in 2018 were reviewed. They were acceptable generally, however, some non-compliances observed during the inspection that was listed in the full report regarding microbiological laboratory management and microbiological testing were addressed by the manufacturer to a satisfactory level.

11. Validation

Process validation

The company had policies, procedures, protocols and reports for process validation and qualification.

A new process validation was performed in 2018 as CAPAs to the deficiencies made in the previous inspection. the process validation protocol, report and PV batches were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding process validation were addressed by the manufacturer to a satisfactory level.

Cleaning validation

Equipment was dedicated to PAS API production. Cleaning procedure for equipment and the analytical method validation for testing a residue were briefly reviewed. No comments were made.

Validation of analytical methods

A compendia method was used for routine testing of WHO grade PAS API except for related substances and residue solvents.

12. Change control

Change control was managed according to an SOP. Several change controls e.g. regarding IR instrument and computerized system validation in the QC laboratory trigged by CAPAs to the observations made in the previous WHO inspection were reviewed. They have been addressed in the CAPAs after this inspection by the manufacturer to a satisfactory level.

13. Rejection and re-use of materials

Reprocessing and Reworking

Procedure for reprocessing and reworking were available for review. Reworking was not allowed as specified. A reprocessed PAS batch was checked and appeared acceptable.

Recovery of materials and solvents

Solvents and mother liquor were recovered and recycled in the PAS production except WHO grade PAS API. This remains the same as previous inspection.

14. Complaints and recalls

Complaints

The complaints were managed according to written procedure. Upon receipt by sale or QA department the complaints should be categorized as critical, major and minor. Since the last WHO inspection, no complaints on PAS API have been received.

Recalls

The company stated that no recall had ever been performed.

15. Contract manufacturers (including laboratories)

Contract manufacturing and routine testing were not applicable to the API, PAS-Na

The PAS polymorph testing and genotoxic impurity testing were contracted to a contract laboratory.

Part 3	Conclusion – Inspection outcome

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, ***Liaoyuan Silver Eagle Pharmaceutical Co., Ltd.*** located at ***No. 2 Wealth Northern Road, Youyi Industry Area of Liaoyuan Economic Development Zone, Liaoyuan, Jilin Province, 136200, China*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

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

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

Part 4	List of GMP Guidelines referenced in the inspection report

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO GMP for APIs or WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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. ***Short name: WHO GMP*** or ***WHO TRS No. 986, Annex 2***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS 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.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. ***Short name: WHO HVAC Guidelines*** *or* ***WHO TRS No. 1010, Annex 8***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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.
   Short name: WHO TRS 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.
   Short name: WHO TRS 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.
   Short name: WHO TRS 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.
   Short name: WHO TRS 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.
    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 production 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. 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 GDRMP guidance or WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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 Multisource guidance or WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf