

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

Part 1	General information
Manufacturers details	
Name of manufacturer	Amsal Chem Private Limited
Corporate address of manufacturer	Kakad House, 'B' Wing, 4th Floor 11, Barrack Road, Bombay Hospital Avenue India-400 020 Mumbai
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Amsal Chem Private Limited A-1 / 401, 402, 403, G.I.D.C. Industrial Estate District Bharuch India-393 002 Ankleshwar, Gujarat GPS coordinates (WGS 84 expressed in decimal degrees): N 27.6173, E 72.997627
Synthetic unit /Block/ Workshop	Block 401 and 403
Inspection details	
Dates of inspection	21-23 November 2018
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	Manufacture, distribution and laboratory testing of APIs, intermediates, drug products and nutraceuticals. Specific types of APIs (i.e. cytostatics, betalactams, biologicals, etc.) or any other specific activity that can impact on the API manufacturing activity were not detected.
General information about the company and site	Amsal Chem Pvt Ltd is a manufacturer of Active Pharmaceutical Ingredients (APIs), and intermediates, catering to the Indian, as well as export markets. The company has to its credit a history of over twenty-three years in the manufacture of the APIs. The company is regularly supplying its products to Multinationals, major Government & Semi-Government Organizations and Formulators, and exports its products to Asian countries. It is considered as the largest Isoniazid manufacturer worldwide.
History	The site was inspected by the following authorities: - Korea November 2017; - WHO pre-qualification (PQ) August 2016; - EDQM October 2014; - WHO pre-qualification (PQ) 2013; - WHO Prequalification (PQ) /MHRA 2012; - WHO Prequalification (PQ) 2005.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	A joint WHO-EDQM inspection was performed in the framework of the CEP dossier for the manufacture of Isoniazid R0-CEP 2013-029-Rev 00 and of the APIMF 005 regulatory dossier registered with WHO for Isoniazid.
Restrictions	None
Out of scope	Other than Isoniazid
WHO APIs covered by the inspection	Isoniazid (APIMF005)
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
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 (where applicable)
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1. Quality management

The quality management systems were established, documented and implemented in general. The QA and QC department was independent from production. The production and quality control procedures were defined in detailed procedures (SOPs) and were followed.

The following documents related to Annual product quality reviews was reviewed during the inspection:

- Annual product quality review of Isoniazid for 2017; 375 batches produced.
- Annual product quality review of Isoniazid for 2016; 401 batches produces.

The SOP for handling of the deviation was reviewed. Deviations arising out of testing were handled through OOS procedure. The deviations were classified into incidents, minor, major and critical deviations - see major deficiency D2. Minor Deviation Record Registers for 2017 and 2018 were reviewed. It was noted that some of the problems concerning maintenance were recurrent (e.g. line/jacket leakage, problems with oil or water boiler etc.).

The SOP for release/rejection of finished goods was reviewed during the inspection.

The SOP for internal audit was reviewed during the inspection, together with the internal audit planner for 2018 (two cycles, March & September 2018) and the Internal audit summary report of the year 2018 (cycle 1).

Issues noted from this section have been addressed and will be verified during future inspections.

2. Personnel

According to the records reviewed and interviews held there were an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs. The following documents with regard to training were reviewed during the inspection:

- SOP for training;
- Training attendance record for 5 helpers of production on several SOPs for cleaning;
- Examples of Certificates of external training:
 - o Warehouse officer trained by Warehouse Watch on Warehouse safety awareness;
 - o Safety consultant & trainer, member of L.K. Dungrani Safety Training Institute, provided training on awareness of general plant safety; certificates issued to several staff members.
- Training feedback & evaluation record of a helper.

Issues noted from this section have been addressed and will be verified during future inspections.

3. Buildings and facilities

The manufacturing facility was broadly divided into three blocks as 401, 402 and 403. Isoniazid was produced on block 401. Buildings and facilities used in the manufacture of intermediate and Isoniazid were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. It was however noted that the facilities did not have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination. Laboratory areas and operations were separated from production areas. Buildings used in the manufacture of Isoniazid was not properly maintained, repaired and kept in a clean condition as noted on several instances.

The SOP for facility and building maintenance was reviewed, together with the Building maintenance history logbook (including both blocks).

A building maintenance log was kept, for all interventions on buildings not falling under preventive maintenance for utility and equipment.

The reverse osmosis (RO) & purified water plant, as well as the raw water underground tank (supplied by the Gujarat Industrial Development Corporation - GIDC) were visited. The water underwent treatment at the RO Unit, the carbon filter, cation and anion exchange columns. After these steps, water was passed through a mixed bed and filtered (10 µm filter) before going into the PW storage tank. The two purified water distribution loops supplying to Block 401 and Block 402 had additional measures to control microbial load: filtration (5, 1 and 0.45 µm) and 2 UV lamps equipped with intensity meters. Online conductivity was monitored and recorded. The sanitization was performed once every fortnightly at 95°C for 1 hour. Logbooks was maintained and verified.

Issues noted from this section have been addressed and will be verified during future inspections.

4. Process equipment

The equipment maintenance calibration and cleaning were performed according to the procedure in general. Various reactors of stainless steel, mild steel and glass reactors were used by the facility. Production equipment were used within the qualified operating range. Major equipment (e.g. reactors, storage containers) and permanently installed with processing lines used during the production for an Isoniazid were appropriately identified.

A routine cleaning was applied between batches. A more extensive cleaning (thorough cleaning) was applied only every 6 months.

Issues noted from this section have been addressed and will be verified during future inspections.

5. Documentation and records

The company had a documentation system in place consisting of organization charts, SOPs, protocols, records, reports, etc. SOPs and specifications for the product existed. Documents related to the manufacture of intermediates or APIs were prepared, reviewed, approved and distributed according to a written procedure.

Batch production records were prepared for each intermediates and API and included complete information relating to the production and control of each batch.

Laboratory control records included complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays.

The SOP for BPCR issue and controlling for manufacturing products was reviewed.

The batch record for Isoniazid was reviewed: the crude batches corresponding to this batch were INHC/693/2017, INHC/694/2017, INHC/65/2017 and INHC/696/2017. The batch was reprocessed into batch 17318/INH, which was finally released.

Issues noted from this section have been addressed and will be verified during future inspections.

6. Materials management

There were written procedures describing the receipt, labelling, quarantine, storage, and handling of materials, as well as the procedures for sampling, testing and approval or rejection of materials. The materials were received using a checklist by the warehouse personnel. A manual system was in place to record inward receipt of the materials. The status labels were prepared by the warehouse personnel (yellow for understand and green for approved materials). A copy of the approved supplier list was available which confirmed that 4-Cyanopyridine was procured from two different sites of Vertellus. Weight verification was performed on the incoming materials using $\sqrt{n}+1$. Sampling was also performed using $\sqrt{n}+1$ principle, if less than 5 containers were received, all containers were sampled. Two data loggers were used to monitor and record the temperature of the warehouse.

A separate area was available for the return and rejected materials which was under QA access control. Sampling and dispensing room was consisted of separate material and personnel entry. Logbook was maintained for sampling, dispensing and cleaning of the area. Balance used for sampling and dispensing was daily verified. It was also noted that small quantity of liquid were also dispensed from the same sampling & dispensing area.

TCS-ion, an inventory management system was currently under installation.

Finished goods store for non-isoniazid materials was briefly inspected. The room housed materials such as Niacinamide, Chromium picolinate, Niacin, Nicotinic acid, Pyrazinamide, Amlodipine Besilate and Desloratadine. It was noted that adequate physical segregation was not performed to ensure mix-up of different APIs.

The warehouse was found over crowded as adequate space was not provided to store materials in an orderly and secure manner which could lead to mix-up and contamination.

The SOP for supplier's approval procedure was reviewed. The procedure described the process for the evaluation of suppliers and manufacturers for raw materials and packaging materials and categorized raw materials as either generic or key.

The key starting material for Isoniazid is 4-Cyano Pyridine (4-CP) which is procured from Vertellus based in the USA and China. Vendor qualification report of Vertellus Specialty Chemicals (Nantong) Co. Ltd., China for 4-Cyanopyridine was reviewed. The supplier was qualified using the supplier questionnaire forms and on-site assessment by the QA Manager (together with the company's managing director) on 20th June 2016.

Methanol was recovered from several steps in the manufacture of isoniazid. The effluent from the recovery column was collected in the open, thus presenting a risk of contamination.

Issues noted from this section have been addressed and will be verified during future inspections.

7. Production and in-process controls

Production processes were guided by documented procedures and instructions. Production processes including synthesis, purification, crystallization, drying, milling etc were conducted in a dedicated facility. Clean areas were available for the final steps of the API's manufacture, such as isolation, drying, milling, sifting, and packaging. There were in-process controls conducted at appropriate stages of the synthesis to monitor performance of the process and quality of the intermediates and APIs.

Two different manufacturing routes were used for Isoniazid: the one of the approved CEP and the one from γ -picolinic acid, which was marketed only locally, and had been practically discontinued in 2018. The Isoniazid CEP process comprises 3 stages: (1) production of isonicotinic acid amide / INAA from 4 cyanopyridine, (2) isolation of crude isoniazid with use of hydrazine hydrate and methanol and (3) purification with the use of activated carbon, purified water and methanol. The final batch size is 1000 kg. The production takes place in a dedicated facility (block-401).

Washing facility was provided before entering the synthetic production area of Isoniazid. 4-Cyanopyridine was transferred to the production area through elevator, and steam was used to melt it before being transferred to the reactors (R-101 and R-102). It was claimed that R-101 was constructed of stainless steel however it was found rusted and corroded. At the time of the inspection, R-102 was in operation wherein Batch No 326/INAA was being refluxed for 8 hours. The temperature was recorded every hour. Vacuum gauges and temperature sensors were found to be calibrated by Hi-Tech and were within operating range. In addition to these two reactors, other reactors such as R-103, R-118, R-104 and R-105 were used for various unit operations. The SOP for cleaning of reactors and agitated nutch filter (SOP/PRO/03) was briefly sighted and noted that the procedure did not provide step by step for the cleaning of reactors for batch to batch cleaning. R-104 was claimed to be cleaned, upon inspection it was found rusty from inside. Cleaning of the reactors was not adequately performed using appropriate tools such as torch.

The output of the first stage (Isonicotinamide intermediate) was stored inside the production area. It was noted that each lot after centrifugation was tested for moisture content and a pooled sample was tested for complete analysis. Different lots and batches with different status (under test, approved) were stored together without adequate physical segregation. Ambiguity was noted for the status of intermediate. The stage-II output (INHC crude) was stored in stainless steel containers. It was claimed that holding time was established for 30 days, however there was no information available on the label.

Crude isoniazid was further processed in reactors R-108, R-109 and R-110. The crude material was charged to the reactor through the manhole. Stage-III was performed in R-106. It was noted that there instructions and physical barriers were provided before materials were charged to the reactors through manhole. Methanol was recovered and used back in the process. Reactors (R-119 and R-120) were used for recovery of mother liquor. Upon inspection of the crystallizer, a piece of cloth was found inside the crystallizer.

Before entering to the clean area of isoniazid, a sink was provided for washing of hands. Shoe cover and over gown were provided to the visitors. The doors were poorly maintained as yellow stained were observed in most of the doors inside the clean area. The clean room was equipped with discharge valve of the agitated nutch filter (ANF-1), three vibratory sifters, multi-mill and micro pulveriser. From the condition of the sampling port of the ANF as well as non-availability of the accessories to open it, it appeared that the sampling port was not used for some time hence found in dirty condition. The return filter (AHU-13) was obstructed with a weight box and floor balance. There was no provision provided to contain dust where packaging activity was performed.

In general, the production and packaging areas were inadequately maintained and several issues of poor cleaning and functioning of the area were noted (see deficiencies under Building and Facilities & Process Equipment).

Issues noted from this section have been addressed and will be verified during future inspections.

8. Packaging and identification labelling of APIs and intermediates

Packaging and identification labelling of APIs and intermediates were undertaken following a written procedure describing the receipt, identification, quarantine, sampling, examination, release and handling of packaging and labelling materials. Containers provided adequate protection against deterioration and contamination of the intermediate and API that could occur during transportation and recommended storage.

Issues noted from this section have been addressed and will be verified during future inspections.

9. Storage and distribution

The company had separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. Handling and storage of materials was performed in a manner to prevent degradation, contamination and cross-contamination. Materials were stored in fibre drums, bags or boxes off the floor and suitably spaced to permit cleaning and inspection.

Temperature mapping reports had been performed for the new API finished product store area (Block 403) by the third party Hi-Tech Calibration in June 2018 for 24 hours, and for room number 129 and 130 (Block 401) by Cosine Calibration & Testing Laboratory in September 2014. They were both reviewed during the inspection.

Finished isoniazid was shipped in HDPE container for the export markets whereas fiber containers used for the domestic market.

Issues noted from this section have been addressed and will be verified during future inspections.

10. Laboratory controls

The quality unit was independent of production. Documented procedures were in place for sampling, testing, approval or rejection of materials and recording and storage of laboratory data. Appropriate specifications for APIs were established in accordance with accepted standards.

The head of the laboratory was Mr Umesh Patel. He was supported by 2 microbiologists, 3 instrument operators, 8 chemists, 2 raw material chemists, and 2 finished product chemists. The laboratory was equipped with UV-VIS, FTIR (ATR technology), two GC sets with head space and two HPLC sets (EZ-Chrom). Equipment calibration status was displayed on white board.

Although, all the laboratory equipment and instruments were running on standalone computer systems, it was noted that date/time stamp was locked in the HPLC system. The administrator privileges were given to IT personnel. Three levels of privileges (analysts, shift supervisor and administrator) were assigned. Backup was performed by the IT personnel and data were saved on a daily and quarterly basis. Daily back up was performed in portable hard disk whereas quarterly backup was performed on two DVD and stored in two different places (head office and site QA). It was claimed that data were restored on a quarterly basis and verified.

Sample inward register was maintained for incoming raw materials, in-process, intermediates, finished product and stability samples. The laboratory did not have a system to assign unique analytical reference number to the incoming samples.

The analytical raw data of Isoniazid finished product were verified during the visit at the QC laboratory. The batch was exported to China Chimo Pharma Co Ltd. The HPLC system was used for related substance test. The source data of residual solvents for Batch No 18227 were verified on GC and found satisfactory. Date/time stamp of the GC system was found to be locked.

The SOP for water sampling establishes that all use points are sampled weekly and the return points and storage tank are sampled daily. In the sample entry logbook it is noted that some sampling points are not always sampled weekly, but every two weeks (e.g. point SP-12, sampled on 01/11 and 15/11; sample point SP-14, sampled on 3/11 and 17/11). No deviation has been raised. Purified water results in the annual report of 2017 and the monthly results for July 2018 were reviewed (Purified water trend data of block 401, APQR 2017, microbial and chemical testing). Interestingly, the microbial quality of inlet water was not much improved by the RO Unit, the carbon filter, cation and anion exchange columns. Microbial results of the sampling point in the water storage tank (SP-3) were good and no adverse trending was detected in the annual review for 2017, neither in the month results for July 2018.

The samples processed in the microbiological laboratory were Active substance and purified water samples. Media are prepared in-house, following and established SOP. Media fertility of R2A was checked using *Pseudomonas aeruginosa* and *Bacillus spizizenii* (actually *B. subtilis* subsp. *spizizenii*, see deficiency D23). The SOPs for media preparation and for sampling and micro testing of purified water were also reviewed.

The SOP for handling of out of specifications and the Out of specifications records register 2016-2017 and 2018 were reviewed, together with the following OOS investigations:

- OOS/01/2016, pyrazinamide; OOS was invalidated.
- OOSs due to level of diisonicotinoyl hydrazine impurity in isoniazide: OOS/06/2016 (batch 16345/INH), OOS/07/2016 (batch 16355/INH), OOS/05/2017 (batch 17172/INH, also OOS for total impurities, reprocessed into batch 17182/INH), OOS/10/2017 (batch 17298/INH).

The current batch of the Isoniazid Chemical Reference Standard (CRS) was being kept at the Quality Control Laboratory.

Issues noted from this section have been addressed and will be verified during future inspections.

11. Validation

The following documents related to validation and qualification were reviewed during the inspection:

- Validation master plan (VMP) version 07 dated 1/11/2017;
- Equipment validation matrix for isoniazid area (block 401);
- DQ, IQ and OQ protocol of the Agitated Nutsche Filter ANF-1;
- Performance qualification report of pure isoniazid equipment reactor (R-106, R-107), pressure filter PF-1 and PF-2 and agitated Nutsche filter (ANF- 1).
- Concurrent process validation protocol dated 24/10/2016 & report dated 25/11/2016 of Isoniazid due to the change of the 4-Cyanopyridine manufacturer from the USA to the Chinese site of the supplier;
- Isoniazid concurrent validation of 4-CP to INH and recovery process protocol dated 8/8/2018

Issues noted from this section have been addressed and will be verified during future inspections.

12. Change control

The Handling of change control was reviewed, together with Change controls for renovation of block 402 as per GMP requirements (finally not implemented, see major deficiency D1) & CC-011/PRO/2017 (14/03/2017) for replacement of stainless steel reactor RK-114 in block-402 (reactor installed but not in use yet).

Issues noted from this section have been addressed and will be verified during future inspections.

13. Rejection and re-use of materials

The SOP for handling of returned goods was reviewed, together with the Return material record register 2015-2018 and the report of returned material RG/001/2017: the returned drums tested and found compliant, the quantity was repacked.

Issues noted from this section have been addressed and will be verified during future inspections.

14. Complaints and recalls

The SOP for complaint handling was reviewed, together with the following examples of complaint investigations:

- Complaint for Isoniazid batch 17104/INH, manufactured on 03/04/2017: customer Svizera Labs, Mumbai found one container with broken top & two with oil marks and broken seal; 3 drums were returned on 09/05/2017 (return RG/001/2017).
- Complaint for Isoniazid batches 17104/INH & 17112/INH, manufactured on 1st & 24/04/2017: customer Lupin Ltd. found two drums in wet condition from bottom side; 2 drums were returned on 15/05/2017 (return RG/002/2017).

Issues noted from this section have been addressed and will be verified during future inspections.

15. Contract manufacturers (including laboratories)

Not applicable.

Part 3	Conclusion – Inspection outcome
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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, **Amsal Chem Private Limited**, located at **A-1 / 401, 402, 403, G.I.D.C. Industrial Estate, District Bharuch India-393 002 Ankleshwar, Gujarat** 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
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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 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 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. 961, 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.
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