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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Manufacturers Details	
Company information	
Name of manufacturer and address	**Hetero Labs Limited (Unit- III)** Survey No. 120&128, 150/1, 151/2, 158/1, 150 (Part) N. Narasapuram (Village), Nallamattipalem (V), Nakkapally (Mandal), Visakhapatnam (Dist.). PIN : 531 081 Andhra Pradesh, INDIA. $17^0$22'50.70"N $82^0$43'07.72"E 91-583-8368
Corporate address of manufacturer	Hetero Corporate 7-2-A2, Industrial Estate, Sanath Nagar, Hyderabad – 500018 Telangana. INDIA. Tel. : 0091-40-23704923 / 24/25 Fax : 0091-40-23704926
Inspected site	
Address of inspected manufacturing site if different from that given above	As above
Manufacturing blocks	Production blocks E, I, P, J, Intermediate Drying Section (IDS) - I
Manufacturing license number	08/VP/AP/2009/B/R
Inspection details	
Dates of inspection	9 October - 11 October 2017
Type of inspection	Initial
Introduction	
Brief summary of the manufacturing activities	The manufacturer was involved in the manufacturing, packaging, labeling, testing and storage of intermediates

<table>
<tr><td>General information about the company and site</td><td>M/s Hetero Labs Limited was incorporated under the Companies Act. 1956 in the status of limited company. The Company was established to manufacture and market a range of organic intermediates; total captive consumption to Hetero group of companies.

Hetero Labs Limited Unit-III started its functions in 2009.
Unit-III has the capability for reactions like Acylation, Addition, Alkylation, Amidation, Amination, Halogenation, Cyanation, Cyclisation, Diazotisation, Enantiomeric Resolution, Esterification, Friedel–Crafts Reactions, Hydrogenation, Halogen exchange, Oxidation, Reduction, Nitration, Peptide Synthesis etc.

Production and in-process control was organized in three shifts covering 24h.</td></tr>
<tr><td>History</td><td>This was the first WHO inspection.

The site has been inspected by the following authorities:
<table>
<tr><th>Authority</th><th>Date/s of inspection</th><th>Facility/block/unit covered by inspection</th></tr>
<tr><td>USFDA</td><td>August 2014</td><td>Current production in Production Block P, FDA visited HLL-III(A)</td></tr>
<tr><td>Drug Control Administration, Government of Andhra Pradesh, India</td><td>June 2017</td><td>Facility</td></tr>
<tr><td>ISO 9001: 2015</td><td>February 2016</td><td>Facility</td></tr>
<tr><td>ISO14001:2015</td><td>February 2016</td><td>Facility</td></tr>
<tr><td>OHSAS 18001: 2007</td><td>February 2016</td><td>Facility</td></tr>
<tr><td>ISO50001: 2011</td><td>February 2016</td><td>Facility</td></tr>
</table></td></tr>
<tr><td>Brief report of inspection activities undertaken</td><td></td></tr>
<tr><td>Scope and limitations</td><td></td></tr>
<tr><td>Areas inspected</td><td>• Pharmaceutical Quality System
• Documentation system
• Production System
• Facilities and Equipment System
• Laboratory Control System</td></tr>
<tr><td>Restrictions</td><td>N/A</td></tr>
<tr><td>WHO product numbers covered by the inspection</td><td>Intermediates for the following APIs
• APIMF 297 Sofosbuvir
• APIMF123 Lamivudine Anhydrous
• APIMF 184 Atazanavir Monosulphate</td></tr>
</table>

Abbreviations

AHU	Air Handling Unit
ALCOA	attributable, legible, contemporaneous, original and accurate
AQL	Acceptance quality limit
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
FG	finished goods
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
ID	identity
IR	infrared spectrophotometer
IPC	In process control
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
NIR	near-infrared spectroscopy
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	preliminary hazard analysis
PM	preventive maintenance

PpK	process performance index
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
RM	raw materials
RS	reference standard
SAP	system applications products for data processing
SFG	semi-finished goods
SOP	standard operating procedure
STP	standard test procedure
T	temperature
TAMC	total aerobic microbial count
TFC	total fungal count
TLC	thin layer chromatography
TMC	total microbial count
TOC	Total organic carbon
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
WFI	water for injection
WS	working standard

Part 2	**Brief summary of the findings and comments (where applicable)**

Brief summary of the findings and comments

1. Pharmaceutical quality system

The quality management system was generally well established, documented and implemented; the system encompassed the organizational structure, procedures and processes. QA and QC departments were independent of production. In general, deviations from established procedures were documented and explained.

The SOP “Data integrity policy” was discussed. SOP training schedule was presented to inspectors.

Product Quality Review (PQR)
The corporate SOP "Preparation of annual production product review report (APQR)" was discussed.

Separate APQR was prepared for general systems. APQR was performed annually and according to the SOP should be completed by the end of February of the following year.
Process capability was evaluated by statistical process control (SPC) by Cpk. Process capability was calculated using Minitab software.

APQRs for Sofosbuvir intermediate, Lamivudine Anhydrous intermediate were discussed:

The corporate SOP "Continued process verification" was discussed. Cpk was applicable for the following process parameters:

- Yield
- Quality parameters as:
    - Chromatographic purity by GC
    - Chromatographic purity by HPLC
    - Assay

Cpk value	**Process capability**
<1.0	Process is capable
1.0	Process is just capable
1.0 – 1.33	Process is quite capable
>1.33	Process is highly capable

Quality risk management (QRM)
The corporate SOP "Quality risk management" was discussed. The tool used by the company in managing risk was specified as:

- FMEA, scoring numbers were specified from 1-5. FMEA was used for equipment and facilities and could be used to analyze a manufacturing operation and its effect on product process
- HACCP
- HAZOP

"Quality risk assessment report for Sofosbuvir intermediate was discussed.

Deviations
The corporate SOP "Handling deviations and incidents" and register were discussed. The SOP was applicable to all deviations and incidents related to quality system. According to the SOP, deviations and incidents should be trended every three months.

A number of deviations /root cause analysis associated to CAPA reports were discussed.

Laboratory incidents

The corporate SOP "Handling of laboratory incidents" and register were discussed. The SOP was applicable for all laboratory errors occurred during sampling, analysis / calibration or found during online review. Incidents were categorized as:

- Type I – human error
- Type II – malfunction of instruments
- Type III – other errors, for example unexpected UPD/power failure, STP errors, software errors

Root cause investigation

The corporate SOP "Procedure for investigation" was discussed. The following tools were used:

- Brainstorming
- 5 Why`s
- Fishbone diagram

Corrective actions and preventive actions (CAPA)

The corporate SOP "Corrective and preventive actions", and register for 2017 were discussed. The SOP was applicable but not limited to:

- Deviations
- Incidents
- OOS/OOT
- Complaints
- Recall
- Risk assessments
- Returns
- Or any other actions related to improvements.

CAPA implementation and effectiveness review was performed by QA and reported during management review meetings.

According to the SOP, CAPAs were proposed by cross functional team. CAPA implementation was monitored by QAD personnel.

Change control (CC)

The corporate SOP "Change control, and registers were discussed. CC registers were specific to product and department. Impact assessment and risk evaluation was applied to CC. CCs were categorized as:

- Minor
- Major
- Temporary
- Permanent

CC implementation was reviewed quarterly by QA.

A number CCs (production department) were discussed.

Management review (MR)

The corporate SOP "Management review" was discussed. According to the SOP, management reports were prepared monthly. Standard agenda was specified. MR was to be performed every 3 months. Last MR minutes and schedule were presented to inspectors.

According to the SOP, QAD shall forward the summary report to Head Corporate Quality. Head Corporate Quality reviewed the summary report and provided guidance when required.

Complaints

The corporate SOP "Handling of customer complaints", its flow chart, register and trends were discussed. Complaints were categorized as:

- Critical
- Major
- Minor
- Established
- Non-established

According to the SOP, complaints should be trended every 3 months. Complaint registers were product related.

Site Deputy General Manager QA (Head QA) was responsible for complaints investigations.

A number of complaint investigation reports were discussed.

Recalls

The corporate SOP "Product recalls" was discussed. There were no product recalls in the site history. Recall effectiveness was evaluated by mock recall. According to the SOP, mock recall should be performed every three years. Site Deputy General Manager QA (Head QA) was responsible for handling recalls. Intermediates were supplied only to site of Hetero Labs and Hetero Drugs API.

Returns

The corporate SOP "Handling of returned goods" and registers were discussed. Registers were product based. A number of returned goods notices were discussed.

Self-inspection

The corporate SOP "Internal audit" and schedule for 2017 were discussed. The following departments were listed under self-inspection programme:

- Warehouse
- Production
- Engineering
- Quality control
- Quality assurance
- Human resources
- Plant R&D

According to the SOP all department should be audited once in six months. Spot checks showed that schedule was followed. Self-inspections were performed using department wise checklists.

Quality control department self-inspection report was discussed. The scope of self-inspection was:

- Receiving and testing samples
- Equipment qualification
- Equipment calibration
- Reference standards / working standards / impurity standards / primary standards
- Retained samples
- Stability samples
- Water samples analysis
- SOPs & records
- General
- Data integrity
    - Instruments
    - Sample set
    - Audit trail

Supplier qualification

The corporate SOP "Vendor qualification" and its flow chart and vendors audit schedule for 2017 were discussed. The SOP was applicable for raw materials, chemical substances, catalysts, reagents, solvents and packaging materials vendors. Approved suppliers list was presented to inspectors.

According to the SOP, API starting materials / intermediate vendors / primary packaging materials vendors should be audited every 3 years. Audits were performed by teams composed of CQA and site QA.

Contracts

Quality Agreement with "BMB vendor "Juangxi Sunfull Chemicals Co Ltd" discussed.

Personnel

The current organization chart of the company was available. The company had sufficient number of personnel with responsibilities according to their respective unit and department.

According to Company's presentation, the site employed approximately 1065 full time employees:

Personnel were wearing suitable clothing for the manufacturing activities.

The corporate SOP "Training" and GMP training schedule were discussed. According to the SOP, all new recruits should be trained for minimum of 60 working days at the time of joining.

The site SOP "Qualification of analysts in quality control laboratory" was discussed. According to the SOP new analysts as well as analysts under re-qualification were given to analyze approved sample, results were compared. RSD values for triplicate tests were specified. Re-qualification of analysts was performed every 2 years. Analysts' competency list was presented to inspectors.

The site SOP "Control of contract workmen" was discussed. Contract workmen training module was available in local language.

Mr. XX from production training records was discussed. GMP training records were kept by QA department and on job training records by concerned department.

Staff member from QC department training records for HPLC analysis were discussed.

Executive QC department job description was discussed.

The site SOP "Health check-up of employees" was discussed. The SOP was applicable for Hetero Unit III employees. According to the SOP, all employees should undergo periodical medical examination once in a year.

2. Documentation system

Documentation system was generally well established.
The corporate SOP "Initiation, approval, revision and distribution of procedures" and SOP "Documentation requirements" were discussed. According to the SOP, SOPs were reviewed every 3 years. Documents retention times were specified.

Documents related to the manufacture of intermediates were prepared, reviewed, approved and distributed according to written procedures.

Documents were stored in QA archive in mobile racks.

3. Production system

In general production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Deviations from procedures were recorded; major deviations were investigated. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use.

The following production blocs were inspected:

Production block	APIMF No	API name
I	APIMF 297	Sofosbuvir
E	APIMF 123	Lamivudine Anhydrous
P	APIMF 184	Atazanavir Monosulphate
J	APIMF 184	Hydrogenation step for Atazanavir Monosulphate

Solvents were delivered in tankers and drums. Samples were taken from tankers, after release solvents were transferred to the storage tanks and mixed with solvent in tank. The site SOP "Receipt, verification, quarantine and sampling of raw materials," was discussed. According to the SOP, samples from all storage tanks shall be tested in the first week of every month from existing stocks.

Solid starting materials were received and stored in the warehouse No 1, ground floor. Packaging materials and were stored in the same building.

Reprocessing and Reworking

According to the SOP section XX "Re-working should not be done for any failed product obtained during manufacturing process and not in the scope of Hetero's API manufacturing process.

Reprocessing (RP) was established in corporate 'SOP'. Unit-III followed the provision in the SOP: "failure batch shall not be subjected for reprocessing by not exceeding three cycles for any similar failure in the same parameter".

Development unit created procedures for reprocessing and reprocessing master batch records.

The site level SOP on hold time studies was discussed. The SOP had been supplemented in 2017 with a provision stating that in case reprocessing was done on earlier stages of the intermediate synthesis, the final intermediate has to be placed on a hold time study. Hold time after reprocessing was a one-off study for a specific intermediate. PQRs reflected the situation with hold time studies. During the running year, change controls could be tracked for information as stated by the Company; reprocessing was accompanied with a change control report.

Blending

The corporate SOP "Blending" was discussed. Unit-III had created intermediate-specific master records for blending. Blending was subjected to intermediate -specific validation and, in case of RPM change, to re-validation. Unit-III had established validation acceptance criteria (RSD), general to all intermediates, depending on blender capacity. Yearly blending logbooks were maintained for specific intermediates.

The Company stated that Sofosbuvir intermediate had not been subjected to blending.

The site level SOP on "Hold time studies" was discussed. The SOP had been supplemented in 2017 with a provision to initiate hold time studies for blended batches.

Recovery of solvents and mother liquors

The site level "Procedure on usage of recovery solvents / recovered materials" was discussed.

Batch numbering

The corporate SOP "Batch numbering system" was discussed.

4. Facilities and equipment system

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups and contamination.

Permanently installed pipework was appropriately identified. Solvents pipelines had different colour codes.

Equipment status boards indicated associated equipment calibration status, due dates and preventive maintenance due dates. Equipment was identified as to its contents and its cleanliness status.

"Temperature mapping study of intermediates warehouse" was discussed.
Separate warehouses were provided for storage of solid raw materials, liquid raw materials and finished intermediates. Sampling and dispensing was done in separate rooms in warehouses. Warehouses seen were clean and in good order.

Qualification and Validation

Process Validation
Corporate 'validation master plan and corporate SOP "Process validation" were discussed. Amendments had been made earlier in 2017 in both documents, including removal of retrospective validation.

Sofosbuvir validation protocol/report was discussed. Cpk calculations were done, as prescribed by the corporate procedure. Routine batch master records had critical operations formatted in 'bold', the respective process parameters were reviewed in PQR. The SOP prescribed 3 validation batches should be used in case of KSM change, unless the vendor was already approved by another Hetero site; in the latter case, an equivalence study was to be performed.

The corporate SOP on continuous process verification was discussed.

Cleaning Validation
The corporate SOP was discussed. A carry-over limit for intermediates was established in the SOP.

Practical cleaning procedures were established on the site level. For batch-to-batch cleaning, general SOPs for equipment types (e.g. reactor) as well as intermediates-specific SOPs by particular equipment ID numbers were available.

The site SOP "Cleaning of new equipment" also covered a general product change-over procedure.

In case of product change-over, separate cleaning records were filled in. The cleaning master record was created for each main equipment item. The master record included step-wise instructions; additionally, respective SOPs were available.

In case of batch-to-batch cleaning, the operation was included in the batch record as "equipment cleaning details record" (no step-wise instruction was written in the record itself (SOP was to be followed), solvents were pre-printed / part of the batch master record).

Computer System Validation
The site SOP "Computer systems validation", effective from 01/09/2017 was available but had not been used till the date of inspection.

LabSolution software validation was performed by vendor on August 2016.

5. Laboratory control system

In process control (IPC) analysis were performed in Quality control laboratory. Incoming samples were recorded in product dedicated sample registers.

The site SOP "Receiving, sampling and testing of samples" was discussed.

HPLCs and GCs were connected to the LabSolutions software, version 6.5. The following instruments were stand alone: UV, FTIR, polarimeter and autotitrator.

The site SOP "Good chromatographic practice", SOP "Integration procedure for chromatograms" and SOP "Review of audit trails", were discussed.

The site SOP "Server with LabSolutions software" was discussed. The level of access was divided into 5 levels, section XX described LabSolutions software back-up data schedule. Daily, monthly and yearly back-up register for 2017 was presented to the inspectors.

The site SOP "QA release of intermediates" was discussed. Release was done using a check list.

The site SOP "Working standards" was discussed. Intermediates working standards were stored at 2°C to 8°C, ambient temperature and in freezer.

The site SOP "Retained samples" was discussed. Retained samples were stored until re-test date, afterwards samples were destroyed.

OOS (out of specification), OOT (out of trend)

The corporate SOP "Out of specification results" and SOP "Out of trend results" were discussed. OOS and OOT paper based log books were presented to inspectors. OOS was applied also to raw materials and recovered / distilled solvents.

A number of OOS reports from 2016 were reviewed. Investigative testing had been conducted.

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 Hetero Labs Limited (Unit- III, production blocks E, I, J and P) Survey No. 120 & 128, 150/1, 151/2, 158/1, 150 (Part) N. Narasapuram (Village), Nallamattipalem (V), Nakkapally (Mandal), Visakhapatnam (Dist.) Andhra Pradesh, INDIA was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for active pharmaceutical ingredients guidelines.

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 used for assessing compliance

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 TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
   Short name: WHO TRS No. 986, Annex 2

3. 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

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

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

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

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

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

9. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
Short name: WHO TRS No. 957, Annex 3
http://www.who.int/medicines/publications/44threport/en/

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

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

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

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

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

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

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

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

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

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

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

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

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

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