World Health Organization

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Prequalification Team Inspection services
WHO INSPECTION REPORT

Desk Assessment
Active Pharmaceutical Ingredients (API) manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Hetero Labs Limited (Unit I)
Corporate address of manufacturer	Hetero Corporate, 7-2-A2, Industrial Estates, Sanath Nagar, Hyderabad– 500 018, Telangana, India
Name & address of manufacturing site	Hetero Labs Limited (Unit I), Survey No. 10, IDA, Kazipally, Gaddapotharam, Jinnaram Mandal Sangareddy District, Telangana, India 502 319
Synthetic Unit/Block/ Workshop	A, B, C, D, E
Start and end dates of review	02 September – 01 October 2019
API covered by this desk assessment	

API	**PQ status**	**Manufacturing Blocks**
Lopinavir	Accepted	C & D
Stavudine	Accepted	Discontinued
Tenofovir disoproxil fumarate	Accepted	E & C
Emtricitabine	Accepted	E, C & D
Lamivudine	Accepted	C
Abacavir (sulfate)	Accepted	C
Zidovudine	Accepted	C
Efavirenz	Accepted	D
Atazanavir monosulphate	Accepted	A
Abacavir (sulfate)	Accepted	C
Sofosbuvir	Accepted	B
Dolutegravir Sodium	Accepted	E, B & D
Daclatasvir dihydrochloride	Accepted	B
Darunavir	Under assessment	A

List of documents submitted according to the company

1. Documentation related to US FDA inspection
2. Documentation related to Health Canada letter
3. List of regulatory inspections during last 5 years
4. Documentation related to EMA inspection
5. Documentation related to OGYEI Hungary inspection
6. COFEPRIS, Mexico GMP certificate and inspection
7. Ministry of industry and trade of Russian federation GMP certificate
8. Declaration on no use of shared equipment between sartan and WHO PQ APIs
9. Documentation related to Pharmaceuticals and Medical Devices Agency Japan GMP inspection
10. Hetero Unit I AHU layouts and purified system layout, site layout
11. SMF dated 27 March 2019

	12. Analytical test reports and BPRs for a. Abacavir sulfate (AB) b. Abacavir sulfate (AV) c. Atazanavir d. Darunavir e. Dolutegravir f. Emtricitabine g. Lopinavir h. Sofosbuvir 13. APQRs 2018 for a. Abacavir sulfate (AB) b. Abacavir sulfate (AV) c. Atazanavir APQR d. Daclatasvir APQR e. Duranavir APQR f. Dolutegravir APQR g. Efavirenz APQR h. Emtricitabine i. Lamivudine j. Lopinavir k. Sofosbuvir l. Stavudine m. Tenofovir n. Zidovudine APQR 2018 14. Batch shifting and packaging records for: a. Abacavir sulfate (DOV) b. Abacavir sulfate (AB) c. Atazanavir d. Daclatasvir e. Duranavir f. Dolutegravir g. Efavirenz h. Emtricitabine i. Lopinavir APQR 2018 j. Sofosbuvir APQR 2018 k. Stavudine APQR 2018 15. List of recalls 16. Self-inspection declaration 17. Out of stock situations 18. Risk assessment report for possible contamination of nitrosamine impurities, dated 25 February 2019 19. Amendment to risk assessment report for Nitrosamine impurities in WHO APIs, dated 27 February 2019 20. 2nd amendment to risk assessment report for Nitrosamine impurities in WHO APIs	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
U.S. Food and Drug	Dates of inspection:	17 – 28 September 2018

Administration	Type of inspection:	Related to Sartan APIs
	Block/Unit/Workshop	Manufacturing Blocks-A, B, C, D, E, H & J, including the General Division where WHO APIs are manufactured
	APIs covered:	• APIs by chemical synthesis
EMA (AIFA Italy)	Dates of inspection:	28 January – 2 February 2019
	Type of inspection:	Full inspection report not received as of 1 October 2019
	Type of inspection:	Post approval
	Block/Unit/Workshop:	A, B, C, D, E, H, J, G, M and ONCOLOGY BLOCKS (F, I, K)
	APIs covered:	• APIs by chemical synthesis
National Institute of Pharmacy and Nutrition OGYEI, Hungary	Dates of inspection:	18 – 22 March 2019
	Type of inspection:	On behalf of EU in order to check the compliance of API to the EU GMP standards
	Block/Unit/Workshop:	• Block A • Block C • Block D • Block F • Block I • Block J • Block K
	APIs covered:	• *APIs by chemical synthesis*
Pharmaceuticals and Medical Devices Agency, Japan	Dates of inspection:	10 – 13 December 2018
	Scope of inspection:	Pre-approval GMP compliance inspection of gefitinib , pre-approval GMP compliance inspection for partial change (added manufacturing site)
	Block/Unit/Workshop:	• Storage area ▪ WAREHOUSE (0): Raw material warehouse ▪ FSA (0) GROUND FLOOR: Finished product warehouse ▪ Solvent tanks • Manufacturing area ▪ I-BLOCK: WET SECTION, PHARMA SECTION ▪ F-BLOCK: WET SECTION, PHARMA SECTION
Part 3		
Date and conclusion of most recent WHO inspection	<u>20 to 24 February 2017</u> 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, a decision on the compliance of HeteroLabs Ltd. Unit-I, 1 Survey No. 10. Gaddapotharam Village, Jinnaram Mandal, Sangareddy District, Telangana, INDIA with WHO GMP guidelines will be made after the manufacturer's response to all of the observations hasbeen assessed. Inspection closing letter, dated 3 January 2018: On the basis of the findings of the inspection and these subsequent responses the inspectors have recommended that the API:	

	1. Lopinavir 2. Stavudine 3. Tenofovir Disoproxil Fumarate 4. Emtricitabine 5. Lamivudine anhydrous (Not covered) 6. Abacavir hemisulphate, 7. Zidovudine (Not covered) 8. Efavirenz (Not covered) 9. Atazanavir Sulphate 10. Abacavir Sulfate (Process-II) 11. Sofosbuvir 12. Dolutegravir Sodium are considered to be compliant with the standards of Good Manufacturing Practices (GMP) for APIs published by the World Health Organization (WHO), for the scope of activities listed below: • Manufacture and packaging of APIs.
Brief summary of manufacturing activities	Production and Laboratory Control of APIs
General information about the company and manufacturing site (according to the latest WHO report)	The site is located in 7-2-A2, Industrial Estates, Sanath Nagar, Hyderabad- 500 018, Telangana, India. There are approximately 1467 employees at the site at the time of inspection. There were 13 Production blocks (A, B, C, D, E, F, G, H, I, J, K, L, M) for pharma-related production: Blocks E, G and M were for intermediates production. Blocks F, I,K and L were for oncology APIs. Penicillin, beta lactam antibiotics and hormones APIs were not produced on this site.
Focus of the last WHO inspection	Production and quality control of APIs
Unit / block / workshop number	Block A, B, C, D and H Production blocks: E/CS-I, VCS-III, IDS, E/PB-11, I/PS-III. Warehouses, including raw material (RM), finished APIs, packaging material, extended WH ("Warehouse 2") for solid material. Water system 1.
Areas inspected	• 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)
Out of scope and restrictions (last WHO inspection)	Inspection was limited to the APIs produced, with WHO grade only. Out of scope: Oncology APIs
WHO APIs covered by the last WHO inspection	• Lopinavir • Stavudine • Tenofovir Disoproxil Fumarate • Emtricitabine • Abacavir hemisulphate • Atazanavir Sulphate • Abacavir Sulfate (Process-II) • Sofosbuvir • Dolutegravir Sodium
Additional products to be covered by this desk assessment:	• Lamivudine • Zidovudine • Efavirenz • Daclatasvir dihydrochloride • Darunavir

Abbreviations	**Meaning**
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
GMP	Good manufacturing practices
NC	Non-conformity
NRA	National regulatory agency
PQR	Product quality review
PQS	Pharmaceutical quality system
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
SOP	Standard operating procedure

Part 4	**Summary of the assessment of supporting documentation**

a) Manufacturing authorization and GMP certificate granted by the local authority:

Manufacturing licence: 25/MD/AP/97/B/R in Form.25, valid till 31/12/2022

GMP certificate: according to Drugs and Cosmetics Act, 1940 and Rules, dated 24.01.2019, valid till 24.01.2022.

b) Site master file (SMF):

SMF No SMF-001-20, effective 27/03/2019 submitted - acceptable, prepared according to the WHO TRS No. 961, Annex 14.

c) List of all the APIs or other products manufactured on-site:

S. No.	Mfg. Block	Section	Names of APIs being manufactured
1	Block - A	Section-I	Darunavir Amorphous, Darunavir Ethanolate, Atazanavir Sulfate, Ramipril, Cilazapril, Maraviroc
		Section-II	Terbinafine Hydrochloride, Levomilnacipran, Milnacipran Hydrochloride
		Section-III	Aripiprazole, Darunavir Ethanolate
		Section-IV	Ramipril, Cilazapril, Bictagravir Sodium, Darunavir Ethanolate
2	Block - B	Section-I	Atomoxetine Hydrochloride, Saquinavir mesylate, Pioglitazone Hydrochloride, Etravirine, Vortioxetine Hydrobromide, Daclatasavir dihydrochloride
		Section-II	Hydralazine Hydrochloride, Dolutegravir Sodium.
		Section-III	Torsemide, Tenofovir, Alafanamide Hemifumarate, Sofosbuvir, Desloratadine, Lamivudine, Emtricitabine
		Section-IV	Finasteride, Dutasteride, Eplerenone

S. No.	Mfg. Block	Section	Names of APIs being manufactured
3	Block – C	Section-I	Tenofovir disoproxil, Simvastatin, Tenofovir Disoproxil Fumarate, Lopinavir, Oseltamivir Phosphate, Zidovudine, Emtricitabine, Quetiapine Fumarate
		Section-II	Escitalopram Oxalate, Nevirapine Anhydrous, Zidovudine, Abacavir Sulfate, Nevirapine Hemihydrate
		Section-III:	Abacavir Sulfate, Tenofovir disoproxil, Emtricitabine, Lamivudine (Form-I), Abacavir, Efavirenz, Zidovudine
		Section-IV	Quetiapine fumarate, Oseltamivir Phosphate, Hydralazine Hydrochloride, Pioglitazone Hydrochloride, Lopinavir
4	Block - D	Section-I	Dolutegravir Sodium, Entacapone, Emtricitabine, Oseltamivir Phosphate, Efavirenz
		Section-II	Lopinavir, Etoricoxib Efavirenz, Lamivudine, Loratadine
		Section-III	Levetiracetam, Emtricitabine
		Section-IV	Zonisamide, Ezetimibe, Entacapone
5	Block – E	Intermediates	Ramipril, Terbinafine Hydrochloride, Dolutegravir Sodium, Pioglitazone Hydrochloride, Ezetimibe, Emtricitabine, Tenofovir disoproxil fumarate, Simvastatin, Cilazapril
6	Block - H	Section-I:	Valsartan, Olmesartan Medoxomil, Irbesartan
		Section-II:	Irbesartan (Form-A)
7	Block - J	Section-I:	Losartan Potassium
		Section-II:	Losartan Potassium
8	Block – G	Intermediates	Escitalopram oxalate, Nevirapine Anhydrous
9	Block - M	Intermediates	Escitalopram oxalate

Anti-cancer Division

S.No.	Mfg. Block	Section	Names of APIs being manufactured
10	Block – I	Section-I	Imatinib Mesylate Form-Amorphous, Gefitinib, Nilotinib HCl, Erlotinib HCl
		Section-II	Imatinib Mesylate (Form-Alpha), Bicalutamide Form H1
		Section-III	Gemcitabine Hydrochloride, Pemeterxide Disodium 2.5 Hydrate, Cyclophosphamide Monohydrate
		Section-IV	Abiraterone Acetate, Capecitabine
11	Block – K	Section-I	Lenalidomide Form H1, Lenalidomide Form-B, Tipracil HCl
		Section-II	Capecitabine, Ibrutinib Form-A,
		Section-III	Imatinib Mesylate (Form-Beta), Afatinib Dimaleate, Capecitabine, Palbociclib
		Section-IV	Docetaxel Trihydrate, Paclitaxel, Bendamustine Hydrochloride, Regorafenib
		Section-VI	Olaperib, Enzalutamide, Trifluridine
12	Kilo Lab	---	Bortezomib (Form-II), Cabazitaxel, Plerixafor, Pralatrexate

S.No.	Mfg. Block	Section	Names of APIs being manufactured
13	Block - F	Section-I	Bexarotene, Bicalutamide (Form-H1), Dasatinib Anhydrous, Sorafinib, Sunitinib
		Section-II	Anastrozole, Azacitidine, Letrozole, Temozolomide, Thalidomide
		Section-III	Cisplatin, Carboplatin, Irinotecan Hydrochloride, Melphalan, Oxaliplatin, Pomalidomide
14	Block - L	Section-I	Busulfan
		Section-II	Axitinib (Form-IV), Trametinib

Manufacturing Block details for WHO API & Sartan APIs

S.No.	APIMF	API	Manufacturing block/workshop	
			Before FDA inspection	After FDA inspection
1	APIMF026	Lopinavir	C & D	C & D
2	APIMF 054	Stavudine	D	Product discontinued
3	APIMF 098	Tenofovir disoproxil fumarate	C & E*	C & E
4	APIMF 114	Emtricitabine	C, D & E	C, D & E
5	APIMF 123	Lamivudine	H	C
6	APIMF 126	Abacavir (sulfate)	C	C
7	APIMF 133	Zidovudine	H	C
8	APIMF 164	Efavirenz	D	D
9	APIMF 184	Atazanavir monosulphate	A	A
10	APIMF 292	Abacavir (sulfate)	C	C
11	APIMF 297	Sofosbuvir	B	B
12	APIMF 322	Dolutegravir Sodium	B, D & E	B, D & E
13	APIMF 349	Daclatasvir dihydrochloride	B	B
14	APIMF368	Darunavir	A	A
15	---	Valsartan	H	H

16	---	Losartan Potassium	J	J
17	---	Irbesartan (Form-A)	D	H
18	---	Olmesartan Medoxomil	D	H
19	---	Candesartan	A	Product discontinued
20	---	Telmisartan	C	Product discontinued

* E-Block is intermediate manufactured block.

On 26 September 2019 company submitted written declaration that there is no usage of shared equipment for manufacturing process and solvent recovery between sartan & WHO PQ APIs and no impact on WHO PQ APIs for carryover / contamination of Nitrosamine impurities.

Regarding batches that were manufactured prior to the changes made to the blocks, solvent recovery and shared equipment: the risk assessment was reviewed for each WHO API.

The method that was used to test for the presence of NDMA and NDEA was provided alongside its validation report.

Overall, the risk for WHO PQ APIs that were manufactured prior changes to the process, is considered to be low and a recall is not considered to be warranted, unless any positive test results for nitrosamines are obtained in the meantime.

d) List of all regulatory inspections performed in the last 3 years and their outcomes:

S. No.	Authority	Inspection months
1	EU GMP (OGYEI - HUNGARY)	March 2019
2	EU GMP (AIFA & AEMPS)	January 2019
3	US FDA	September 2018
		March 2017
4	WHO-Geneva	February 2017
5	PMDA Japan	December 2018
6	DCA (GMP)	May 2018

e) Most recent product quality reviews (PQRs) of the concerned WHO API(s):

Submitted for:

Lopinavir
Stavudine
Tenofovir disoproxil fumarate
Emtricitabine
Lamivudine
Abacavir (sulfate)
Zidovudine
Efavirenz
Atazanavir monosulphate
Abacavir (sulfate)
Sofosbuvir

Dolutegravir Sodium
Daclatasvir dihydrochloride
Darunavir

f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant APIs:

Submitted for:

Lopinavir
Stavudine
Tenofovir disoproxil fumarate
Emtricitabine
Lamivudine
Abacavir (sulfate)
Zidovudine
Efavirenz
Atazanavir monosulphate
Abacavir (sulfate)
Sofosbuvir
Dolutegravir Sodium
Daclatasvir dihydrochloride
Darunavir

g) Master batch manufacturing and packaging records of the APIs of interest:

Submitted for:

Lopinavir
Stavudine
Tenofovir disoproxil fumarate
Emtricitabine
Lamivudine
Abacavir (sulfate)
Zidovudine
Efavirenz
Atazanavir monosulphate
Abacavir (sulfate)
Sofosbuvir
Dolutegravir Sodium
Daclatasvir dihydrochloride
Darunavir

h) Recalls in the past three years related to APIs with quality defects:

Name of the product	Date of Recall initiation	Total No. of Batches Returned till date	Reason for Recall

Valsartan	16/07/2018	17 Batches	Complaint Investigation and recall was initiated after regulatory agency and drug product manufacturer notification for presence of NDMA impurity in Valsartan API.
Losartan Potassium	07/02/2019	12 Batches	Complaint Investigation and recall, was initiated after regulatory agency and drug product manufacturer notification for presence of NDEA impurity in Losartan Potassium API.

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with:
Submitted

j) Copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):
Submitted.

k) Out-of-stock situations:
Submitted.

l) Additional documents submitted:
N/A

Part 5	**Conclusion – Desk assessment outcome**

Based on the previous WHO inspection and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site **Hetero Labs Limited (Unit I)**, located at **Survey No. 10, IDA, Kazipally, Gaddapotharam, Jinnaram Mandal Sangareddy District, Telegana, India 502110** is considered to be operating at an acceptable level of compliance with GMP guidelines for APIs.

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

As the competent authorities **(US FDA and AIFA, Italy)** have yet to reach a final conclusion on the site's level of compliance, the conclusion of this desk assessment may be reassessed if new information is received from the AIFA or USFDA or another stringent regulatory authority.

Part 6	**List of guidelines referenced in this 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 **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 Guidelines or WHO TRS No. 986, Annex 2**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9. **Short name: WHO TRS 1010, Annex 9**
https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1

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

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

6. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

7. Good manufacturing practices: guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. **Short name: WHO TRS No. 1019, Annex 3**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

8. 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/

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 3.
Short name: WHO TRS No. 957, Annex 3
http://www.who.int/medicines/publications/44threport/en/

10. 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

11. 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

12. 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

13. 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

14. 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

15. 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/

16. 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/

17. 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

18. 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

19. 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

20. 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

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 TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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

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

24. 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