20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Unit Inspection services
WHO INSPECTION REPORT
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Mylan Laboratories Limited (Sarigam)
Corporate address of manufacturer	Mylan Laboratories Limited Plot No.564/A/22, Road No. 92, Jubilee Hills, Hyderabad, Telangana, 500096, India
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Mylan Laboratories Limited (Sarigam), Plot No. 1606-1609, G.I.D.C., Sarigam, Tal-Umbergaon, Dist. Valsad, Gujarat, 396 155, India GPS coordinates: 20.2999◦ N 72.8475◦ E D-U-N-S 862627630
Unit / block / workshop number	Building I (manufacturing and packaging) Building II (packaging) Building III (Storage)
Manufacturing license number	No. G/28/1072 and G/25/1476 Oral Contraceptive Pills (Hormonal Solid Oral Dosage forms) and Placebo/ Ferrous Fumarate Tablets (Woman's Health Care)
Dates of inspection	22 – 25 November 2021
Type of inspection	Routine
Introduction	
Brief description of the manufacturing activities	Manufacture, quality control and release of Reproductive Health products (Oral Contraceptives and support placebos/Ferrous Fumarate tablets)
General information about the company and site	Mylan Laboratories Limited, India Operations has its Corporate Office located at Hyderabad, Telangana India. Mylan Laboratories Limited, Sarigam is located in G.I.D.C area on Plot No. 1606 - 1609, State of Gujarat, about 19 km. away from Vapi railway station, and approximately 170 km. from the Mumbai International Airport. Site is engaged in the manufacturing of Oral Contraceptive Pills (Hormonal Solid Oral Dosage forms) and Placebo (Inert)/Ferrous Fumarate Tablets for women Health Care. No other manufacturing activities are carried out at this site. Mylan Laboratories Limited, Sarigam is approved by the Commissioner of Food and Drugs Control Administration, Gandhinagar, Gujarat, India, for manufacturing, packaging, testing, storage and distribution of medicinal products/combination products specified in other than Schedule C, C-1, and X and medicinal products specified in Schedule C and C-1 excluding those specified in Schedule X to the Drugs and Cosmetics rules 1945 under Manufacturing License No. G/25/1476 and G/28/1072.

	The site is located on a 10530 sq. mt. plot and built-up area is approximately 10268.99 sq. mt. The facility includes raw and packing materials warehouse, dedicated and segregated area for the manufacturing and packing. There is no Industrial unit in surrounding area which uses hazardous chemicals or emits emissions which are detrimental to environment.
History	On-site inspection by WHO PQT was performed on 12 to 15 April 2016. The site has been inspected by the following authorities:

Authority	Date/s of inspection	Facility covered by inspection
INFARMED I.P Portugal	7th – 11th November 2016	First Floor Building 1
Food and Drug Control Administration (FDCA), Gujarat	8th - 9th March 2017	Building 1, 2 and 3
National Drug Authority (NDA), Uganda	31st January - 1st February 2019	Building 1, 2 and 3
Food and Drug Control Administration (FDCA), Gujarat	26th - 27th March 2019	Building 1, 2 and 3
Medicines Control Authority of Zimbabwe	21st - 22nd November 2019	Building 1, 2 and 3
National Institute of Pharmacy and Nutrition, Hungary	11th - 14th December 2019	Building 1, 2 and 3
Food, Medicine and Healthcare Administration and Control Authority of Ethiopia	3rd – 5th May 2021	Building 1, 2 and 3

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	See Part 2 below
Restrictions	N/A
Out of scope	Products out of scope of WHO PQ
WHO products covered by the inspection	• Ethinylestradiol/Levonorgestrel Tablet, Sugar coated 30mcg/150mcg • Ethinylestradiol/Levonorgestrel + Placebo Tablet, Sugar coated 30mcg/150mcg + 0mg • Ethinylestradiol/Levonorgestrel + Ferrous Fumarate 30mcg/150mcg + 75mg

Abbreviations	**Meaning**
ADE	Acceptable daily exposure
ADR	Adverse drug reaction
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APQR	Annual product quality review
APS	Aseptic process simulation
AQL	Acceptance quality limit
BMR	Batch manufacturing record

BPR	Batch production record
CC	Change control
CCEA	Complete, consistent, enduring, available
CFU	Colony-forming unit
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
GPT	Growth promotion test
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
IPQA	In-process quality assurance
LAF	Laminar air flow
LIMS	Laboratory information management system
LoD	Loss in drying
MA	Marketing Authorization
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OQ	Operational qualification
PDE	Permitted daily exposure
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
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

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

1. Quality system

Principle

Production and quality control operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were specified in written job descriptions. Product and processes were monitored, and the results were reviewed as part of the approval process for batch release. Regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

TrackWise system was used for:

- QSM
  - Manufacturing investigations
  - Lab investigation
  - CAPAs
  - Complaints
  - CC
  - NOR (notice of rejection)
  - Pre-market supply incidents
  - Quality action system

Data integrity policy

SOP "Management of Data Integrity and data Governance" was discussed. SOP was applicable to paper and electronic records as well as for data generated by third parties.

Product Quality Review (PQR)

SOP "Annual Product Quality Review/Product Review", the PQR Schedule for bulk and finished Products and several PQRs were discussed.

According to the SOP PQR shall be conducted annually on rolling basis. For bulk tablets PQRs were prepared from January to December, for finished products delivered to some countries PQRs were prepared based on the date when MA was granted. For other markets date of first product in the year was considered as bare line for PQR.

Cpk was used for process capability evaluation:

CpK < 1.00	Further documented evaluation as well as action plan is required to incorporate product/process enhancements
CpK between 1.00 and 1.33	Process is under marginally control and could require further documented evaluation as well as an action plan to incorporate product/process enhancements
CpK > 1.33	The process is considered in state of control and capable

Management review (MR)

SOP "Quality System Management Review" discussed. Quality System Management (QSM) review shall be carried out monthly to evaluate suitability and effectiveness of QS. QSM review was carried out by Quality Review Management (QRM) Committee comprising of representatives from each functional departments QA was responsible to coordinate with stakeholders and to schedule meeting. Quality indicator reports were prepared by QA and circulated in advance to the QRM committee members. Standard agenda was specified.

The following documents were discussed:

- QSM review meeting reports
- Quality Indicator review report
- Attendance sheet

Site Quality Council Metrics was presented as excel sheet documents.

Complaints

A system was in place to review complaints and other information concerning potentially defective products. SOP explained actions to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect. Complaints concerning a product defect were recorded with original details and investigated. SOP "Handling of complaints" and complaint registers for 2020 and 2021 were discussed.

A number of complaint investigations were checked. Investigations were carried out using fish bone diagram.

Recalls

A system was in place to recall from the market, promptly and effectively, products known or suspected to be defective. Recall SOP was regularly discussed and updated.

SOP "Product Recall and Withdrawal" was discussed. Till the date no recalls were performed. Recall classification:

- Class I
- Class II
- Class III

According to the SOP Mock recall should be carried out annually for all continent's products has been marketed. Mock recall Continent: Asia, country Malaysia was checked.

Batch release

SOP "Batch Release" and batch release registers for 2020 and 2021 were checked. Responsibilities:

- Production and QA supervisors review of BMR and BPR
- Production and IPQA manager/designee verify BMR/BPR.
- Analytical QA review of Batch Analytical Reports
- Head QA/designee responsible review BMR, BPR and Finished Product CoA before release.

Review of BMR/BPR
"Execution and Review of Batch Manufacturing Record and Batch Packaging Record" was discussed.
Responsibilities:

- Production personnel – review BMR/BPR
- IPQA – review executed BMR/BPR
- Production manager – review final BMR/BPR
- Head QA / designee – ensure compliance with SOP

Reviews were carried out using check lists.

Returned products
SOP "Handling of Returned goods" and returned good registers for 2020 and 2021 were discussed.

Reprocessing and reworking
SOP "Reprocessing and reworking" was discussed. According to the SOP reprocessing was not allowed. According to the SOP reworking was allowed only due to the problems at secondary packaging stage.

Batch numbering system
"Assign Batch Number to Materials and Products" was discussed. SAP system was used for materials management system.

Change control
"Change Management Process" and change registers for 2020 and 2021 were discussed. Changes were classified as temporary and permanent which arises in the existing document / process/ system. Changes were categorized and:

- Critical
- Major
- Minor

According to the SOP risk assessment should be performed for critical and major changes.

Several major CC were discussed.

Deviation management
SOP "Handling of Incident investigation" was discussed. SOP was applicable to:

- API
- Excipients
- Raw materials
- Packaging components
- In-process materials
- Cleaning validation
- EM
- Finished products

Incidents may include but not limited to failure of a product or materials to meet specifications, deviation from procedures, unusual events which occurs during manufacturing/packaging process, any incident related to GxP computerized systems, classified as:

- Critical
- Major
- Minor

According to the SOP manufacturing investigation should be closed within 45 days and incidents within 12 days.

Incidents registers for 2020 and 2021 were checked. Investigation was carried out using fish bone method.

Corrective and preventive actions (CAPAs)

SOP "CAPAs with Effectiveness check" was discussed. SOP was applicable to but not limited:

- Incident reports
- Investigation reports
- Laboratory Investigation Reports
- Complaints
- Recall/Mock recall
- PQR
- Trend assessment
- Regulatory audit /Internal audit
- Customer audit
- Pre-marketing supply incidents
- Quality Risk Management
- Validation/qualification
- Process improvements
- GxP computerized systems

CAPA register for 2020 and 2021 were checked.

Self-inspection

System for self-inspection was in place and provided a minimum and uniform standard of requirements.
SOP "Self-inspection", schedule for 2021 and self-inspection report were discussed. Self-inspection was performed by team consisting of certified self-inspectors. Qualification criteria was specified. According to the SOP at least one self-inspection should be performed each month. Departments were inspected on 6-month basis. Schedule was approved by Head QA /designee. Data integrity was be assessed as part of self-inspection.

Suppliers approval

System was in place for approving suppliers who can reliably supply starting and packaging materials that meet established specifications. SOP "Vendor Management" and approved suppliers list for APIs, excipients and packaging materials were discussed. SOP was applicable for raw materials and packaging materials vendors approval. Vendor qualification was performed by Global Operations Auditing Team. Vendors evaluation was performed annually by corporate based on lots received, approved, rejected etc. RA was performed of API vendors to determine onsite audit frequency. Based on RA vendors were categorized:

- No risk
- Low risk
- High risk

During pandemic remote vendors audits were performed. SOP "Global Operations Auditing – Remote Auditing - GMP" was discussed.

Manufacturer of Ferrous Fumarate API manufacturer remote audit was discussed. Remote audit was performed using Microsoft Teams platform.

Onsite audit of Manufacturer of Cyproterone Acetate API manufacturer was discussed.

Personnel

Company employed sufficient number of qualified personnel to carry the tasks for which the manufacturer was responsible. Individual responsibilities were defined and recorded as written descriptions. Company employed adequate number of personnel with necessary qualifications and practical experience

"Training of Personnel" and training schedule were discussed. SOP was applicable to permanent workers and contract workers. "My University" e-learning system was used. Following trainings were explained:

- Induction
- Introductory
- Job specific
- GxP
- Re-training
- External
- Self-reading

Trainings were planned and unplanned. A number of training records were checked.

SOP "Qualification of Analyst and Reviewer", Analyst Qualification Matrix and List of Specimen Signatures were discussed. SOP was applicable for newly recruited analysts/reviewers and existing analysts/reviewers. Analyst were given to analyze already approved product and results were compared. Acceptance criteria was specified for different tests. Mr. XX qualification file for HPLC (Related substances) was discussed

SOP "Certification of Microbiologist", Microbiologists Qualification Matrix and List of Specimen Signatures and Mr. XX certification file were discussed.

2. Production system

Production operations followed defined procedures. Significant deviations from the initial protocol were recorded and investigated, root causes were determined and CAPAs were implemented where necessary. Checks on yields and reconciliation of quantities were carried out. Access to production premises was restricted to authorized personnel. Production rooms appeared to be well maintained and clean. Stainless steel bins and containers were used for production and storage of in process products. Metal detectors were challenged before and after the batch and every 2 hours during production. Punches/dies rotation was ensured, dimensions checks were performed.

The following batch manufacturing records were discussed.

- Ferrous Fumarate
- Lactose Granules

Manufacturing processes were validated. The validation policy was summarized in the on process validation and in the validation master plan with annexes, such as:

- Critical equipment requalification policy,
- HVAC systems,
- Environmental monitoring,
- Potable water and purified water sampling plan
- Process validation status,
- Area requalification schedule,
- Water system requalification, HEPA integrity schedule,
- Packaging evaluation status

The hold time study program of the semi-finished goods was detailed in SOP 000483760 upon the following phases:

- Dispensed raw materials
- Binder solution
- Blend/granules
- Compressed tablet
- Coating solution
- Coated tablet
- Lactose granule
- Lubricated blend

3. Facilities and equipment system

Production premises were located, designed, constructed, adapted and maintained to suit the operations to be carried out. Premises were cleaned and disinfected according to detailed written procedures, records were maintained. Throughout the facility a lack of space could be seen. Storage areas were very full, e.g. blend store, bulk store. Critical manufacturing equipment were qualified, the measuring devices calibrated. The annual planner was managed in the SAP system.

The qualification documents of the auto-coater and the calibration of the corresponding digital temperature indicator were discussed.

Cleaning validation

The cleaning validation based on the API characteristics, the ADE values, worst case molecule and MACO calculation was done on accordance with SOP "Cleaning validation".

The PDE values tally with the reports received from the Corporate toxicology expert were used.

HVAC

The total number of the air handling units was XX supplying the controlled areas. The AHUs were continuously running except for the filter cleaning period.
The qualification (including environmental monitoring) and filter replacement records of AHU XX supplying Compression X cubicle was discussed.

Environmental monitoring (EM)

SOP "Microbiological Environmental Monitoring in Classified Areas", sampling plan and trends for 2020 were discussed. EM for production area/warehouse/primary packing area was carried out once in two months, for sampling/dispensing booths monthly. Action and Alert limits were established based on historical results.

Purified water system

SOP "Sampling Procedure of Water", "Water Analysis", sampling plan and tends for 2020 and 2021 were discussed. Samples from PW return loop were taken daily, other sampling points were covered monthly on rotational basis. Action and Alert limits to Total bacteria Count was established:

The calculated value for mean + 3 standard deviations was considered as Alert Limit, the calculated value for mean + 6 standard deviations was considered as Action Limit. Action and Alert limits were reviewed and redefined every two years.

Laboratory premises
The laboratory premises were appropriate for testing of raw materials, intermediates, finished products, validation samples, stability samples and environmental samples in separated areas as:

- Wet analysis
- Instrumental analysis
- Stability Chambers
- Retention sample store
- Microbiology laboratory

Computerized systems
The Inventory List of Computerized Systems was available.

The critical computerized systems were validated including the newly implemented systems:

- LIMS for managing the data generated in the QC lab
- Trackwise for Complaints, Change Management, CAPA, Laboratory Investigation Report (LIR), Manufacturing Investigation Report (MIR), Pre-Market Supply Incidents (PMSI), Notice of Rejection (NOR) and Trend Assessment
- Documentum for Management of Standard Operating Procedure Workflow
- SAP system for Quality Management, Production Planning, Material Management, Sales and Distribution, Finance and Controlling, Project System, Plant Maintenance and Warehouse Management.

The TrackWise User management, user list together with the access roles and privileges of DGM_QA were discussed.

4. Laboratory control system
Contract laboratories
Contract giver and acceptor responsibilities were clearly specified. A number of contract laboratories were used for raw materials testing.

Technical agreement with one contract laboratory was discussed. Laboratory was used for different test, mainly GC and AAS tests.

SOP "Empower 3 Chromatography Data Software Operation" was discussed.

OOS investigation records:
SOP and a number of OOS cases were discussed.

Stability program
There was an on-going stability program in place managed in the SAP system according to SOP-Stability Studies (The stability samples were stored in:

- 30^0C/75%
- 30^0C/65%
- 25^0C/60%
- 40^0C/75%

The following documents were discussed related to the quality control laboratories.

- Stability protocol and Summary 2019 and 2021
- Empower Active User List
- SOP-Receipt and Maintenance of Retain Sample
- Verification of retails sample of Zinnia F Batch No. 8129561
- HPLC User Privileges List
- HPLC System Audit Trails with traceability analyst login
- SOP- Analytical Method Validation
- SOP- Analytical Method Verification of Compendial Procedures
- SOP- Analytical Method Transfer
- SOP- Operation and Calibration of High-Performance Liquid Chromatography
- High-Performance Liquid Chromatography Calibration
- SOP-Empower 3 Chromatography Data Software Operation
- SOP- Management of Analytical Standards
- Working standard report and Usage record Ethinylestradiol
- Reference Standard COA Ethinylestradiol USP
- SOP-Code / Location Transfer and Release of Raw Material and Packing Material
- Analytical Report- Ethinylestradiol
- Analytical Report- Zinnia F
- Analytical Report- Femicept Batch
- Specification Ethinylestradiol
- SOP-Management of Data Integrity and Data Governance
- SOP-Empower 3 Chromatography Data Software Operation

Microbiological Laboratory

Microbiological laboratory had separate rooms for Culture handling and Microbial Limit Test. Culture handling was done in Biosafety cabinet, Microbial Limit Tests were carried out in two LAFs.

SOP "Microbial Culture Media Management" was discussed. The laboratory purchased dehydrated medias and "ready to use" medias. Growth promotion test (GPT) was performed upon receipt for every lot/batch. According to the SOP expiry date for "in house" prepared media was 30 days for liquid media and 15 days for solid media. GPT was performed for each autoclave load. Each lot/batch of R2A and SCDA – "ready to use" medias, used for EM and water monitoring were checked for growth promotion properties with in-house water and EM isolates.

Media preparation was recorded in media specific log books. MacConkey media and R2A media preparation and quality control log books were checked.

"Procedure for Handling of OOS in Microbiology Test Results" was discussed. No OOS/OOT were reported in 2020/2021 till the date of inspection.

Autoclave validation was performed annually by third party. Form "Double Door Steam Sterilizer Loading Pattern" was discussed.

5. Materials system

Incoming materials and finished products were quarantined after receipt or processing, until they were released for use or distribution. Materials and products were stored under the appropriate conditions established by the manufacturer. Starting materials and packaging materials were purchased from approved suppliers, approved suppliers list was available in warehouses. Procedure was in place to ensure the identity of the contents of each container of APIs. Materials were stored at a number of locations. Materials management was managed by SAP system.

Shellac USP was stored on cooling chamber, storage T 8 – 15 ℃. T was controlled/recorded twice per day by two T sensors. Chamber was equipped with sound alarm system connected to the engineering department.

Sampling and dispensing of excipients were carried out in two separate rooms, one for sampling one for dispensing. Sampling and dispensing of Ferrous Fumarate was carried out in separate sampling/dispensing room.

Sampling and dispensing of API was carried out in the sampling and dispensing booths of the RM store.

The following documents were discussed:

- "Sampling of Raw Materials". SOP was applicable for APIs and excipients.
- "Sampling of Packaging Materials". Sampling was done according to the AQL. Single sampling plan was used for secondary packaging materials, general sampling level II was used for primary packaging materials which are received in roll form. For roll labels allowed numbers of joints were specified in labels specifications. Defects were classified.

6. Packaging and labelling system

The bulk tablets were blistered, labelled and packaged according to the market upon separate BPRs.
The blistered and packed final products had different FG codes.The packaging processes were validated.

Part 3	Inspection outcome

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, ***Mylan Laboratories Limited, located at Plot No. 1606-1609, G.I.D.C., Sarigam, Dist. Valsad, Gujarat, 396 155, India*** was considered to be operating at an acceptable level of WHO good manufacturing practices for pharmaceutical products 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.

DEFINITIONS

Critical deficiency

A critical deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

Major deficiency

A major deficiency may be defined as a non-critical observation that:

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

Other deficiency

A deficiency may be classified as other if it cannot be classified as either critical or major but indicates a departure from GMP. A deficiency may be other either because it is judged to be minor or because there is insufficient information to classify it as major or critical.

Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as major.

Part 4	List of GMP Guidelines referenced in the inspection report

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

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/

3. 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

4. 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

5. 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

6. 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/

7. 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/

8. 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

9. 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

10. 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

11. 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

12. 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

13. 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/

14. 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/

15. 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

16. 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

17. 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

18. 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

19. 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/

20. 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

21. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***
https://www.who.int/publications-detail/978-92-4-000182-4

22. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. ***Short name: WHO TRS No. 1025, Annex 4***
https://www.who.int/publications-detail/978-92-4-000182-4

23. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. ***Short name: WHO TRS No. 1025, Annex 6***
https://www.who.int/publications-detail/978-92-4-000182-4

24. Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. ***Short name: WHO TRS 1033, Annex 2***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations¨

25. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3. ***Short name: WHO TRS 1033, Annex 3***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

26. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS 1033, Annex 4***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations