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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Optimus Drugs Private Limited
Corporate address of manufacturer	Survey Number 239 & 240, Dothigudem Village, Pochampally Mandal, Nalgonda District, 508 284 Telangana, India
Inspected site	
Address of inspected manufacturing site if different from that given above	Survey Number-239 & 240, Dothigudem (Village), Pochampally (Mandal), Nalgonda (Dist), Telangana, India
Unit / block / workshop number	Block 1, Block 2 and Block 4
Manufacturing license number	The company had a license to manufacture APIs and intermediates for sale by the Drug Control Administration, Hyderabad and Government of Telangana, India 25/NGIAP/2008/B/G dated 10/09/2008 renewed for the period from 10/09/2013 to 09/09/2018.
Inspection details	
Dates of inspection	15-18 August 2016
Type of inspection	Re-inspection
Introduction	
Brief summary of the manufacturing activities	The site was engaged in manufacturing of Active Pharmaceutical Ingredients (drug substances) and Intermediates (drug intermediates). Besides the commercial manufacturing there was an R&D (process development and analytical development laboratory in place. Other than Drug substances (API) and intermadiates manufacturing for pharmaceutical purpose no other manufacturing activity was in place. No penicillines, pesticides, steroids and steroidal hormones were manufactured at the site.
General	Optimus Drugs was established in June 2004 as custom synthesis laboratory. The

information about the company and site	current facility was acquired in 2006 and the construction of multipurpose intermediate and API facility completed on 2010 and started offering APIs to Domestic and other related markets. In 2014 – 2015, focus shifted to regulated markets (DMF filing with EU and WHO started in 2014, DMF filing with USFDA started in 2015, both directly as well as through customers.
History	2014 MFDS (Ministry of Food And Drug Safety, Korea) 2014 COFEPRIS, Mexico 2015 WHO, Geneva 2016 US-FDA 2016 German authority, Upper Franconia
Brief report of inspection activities undertaken	
Scope and limitations	
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) Site visit: Warehouse for solid materials, Warehouse for Liquid materials in drum, Solvent tank farm, Block 1, 2 &4, Quality control laboratories including chemical and microbial.
Restrictions	None
Out of scope	None
WHO product numbers covered by the inspection	APIMF 255 Linezolid APIMF 286 Linezolid

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
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
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
IR	infrared spectrophotometer
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
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control

QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

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

Brief summary of the findings and comments

1. Quality management

Principles
The Quality Assurance team of the site was headed by the QA Head reporting to the Managing Director of the organization. The organizational chart of the quality functions were provided. The departments and personnel responsible for quality assurance and quality control were independent from the production. The Quality Management was responsible to co-ordinate, develop, implement and maintain Quality System of the Company. The main responsibilities of Quality Management included the follows:
- trainings,
- releasing or rejecting of apis / intermediates,
- review of batch production and laboratory control records,
- product quality related investigations (e.g. deviations, changes, quality related complaints),
- approval of product quality related documenbts e.g. bprs, sops, specifications,
- self-inspections / internal audits,
- vendor qualification,
- product quality reviews.

The implementation of a new, harmonized, software based concept of investigations including CAPAs, Change Management, Qality Risk Management, Complaints, OOs was initiated.

Product quality review
The PQRs were prepared according to SOP QA017 and summarized the following information:
- Product General Information.
- Product history
- Manufactured batches
- Complaits, Returns, recalls
- Validation/qualification statuses
- Stability program

- Change controls
- Non-conformities
- Regulatory filing,
- CAPAs

There were 4 different manufacturing processes (product codes) in place for Linezolid API:
- OP-80 (Route 1) - APIMF 255
- OP-LIZ (Route 2) - APIMF 286
- OP-LID (Route 3)
- OP-LIZ-F1(Route 4)

Product Quality Review 2015 for OP-80 and Product Quality Review 2014 for OP-LIZ were reviewed and discussed.

Finished APIa were sampled and analyzed by Quality Control as per the approved procedures. The QA head and the Deputy QA head were responsible for the product release of APIs and sealable intermediates.
The batch release records of linezolid were discussed, including,
- Test requisition form
- BPR approved by QA
- CoA issued
- Dispatch requirement/Purchase order/Packaging record issued/Batch dispatch

Quality risk management
QRM had been implemented through a SOP. It was the responsibility of QA to oversee implementation of QRM and the responsibility of each Department to execute the SOP.

A risk assessment for block 4 intermediate operation area had been conducted. Risk assessment report for block 1 and 2, and block 3 and 4 have been planned but have not performed at the time of inspection. Non-compliances observed during the inspection that was listed in the full report regarding quality risk management were addressed by the manufacturer to a satisfactory level.

Deviation
A procedure for handling deviation was reviewed. There were three types of deviations mentioned in the procedure: critical, major and minor. Investigation to critical deviation was required by the procedure. The deviation review 2015 showed that 62 deviations in the year divided into categories of man, machine, method, procedure and schedule. Non-compliances observed during the inspection that was listed in the full report regarding deviation were addressed by the manufacturer to a satisfactory level.

CAPAs
A SOP for CAPA management was available for inspection. CAPAS regarding OOS, change control and complaint were under the individual procedure without a comprehensive CAPA system at the time of inspection. Non-compliances observed during the inspection that was listed in the full report regarding CAPA management were addressed by the manufacturer to a satisfactory level.

Self-inspection
A SOP for internal audit/self-inspection was available for inspection. Self-inspection was performed once every six month. The annual plan of self-inspection 2016 was checked. Self-inspection planned in January and July 2016 has been implemented. The July inspection performed covered most of the department from 18 to 30 July 2016. A summary of deficiencies was available.

2. Personnel

Personnel qualifications
An organization chart was available to show the structure and function of the departments. There were approximately 336 employees in total at the time of the inspection.

There appeared to be a sufficient number of personnel to perform GMP related activities, with the education of key personnel including appropriate tertiary qualifications. Contract workers were used in different areas, mainly for housekeeping and material transfer.

The job descriptions were in-line with the organization charts. The job descriptions of the following personnel were reviewed and generally found satisfactory.
- Head QA
- GM QC
- GM Production
- Assocciate Director engineering and utilities
- Senior executive, IT
- Deputy manager QC

Personnel hygiene
There were appropriate provisions for changing into protective clothing and hand washing before entry to production areas. The type of protective clothing, including head and face covering, was appropriate to the activities being undertaken.

Training
Training needs were identified depending on the job responsibilities of the employee by department and QA head. New employee were given induction training including introduction to the company, products, policies and general concept of Good Manufacturing Practices and Quality Management System.
On the job training took place usually under the guidance of immediate supervisor or department head. Efficacy of training was assessed. Training records and qualifications were available for the deputy manager QC.

HR department was responsible for the health and hygiene requirements of employees in the organization with the help of external agency. The pre-employment medical examination was applicable to all levels of employees. Periodic medical checkup was carried out for all the personnel in the organization. The health clearance statement made by a Company physician for the newly hired Dy QC manager was available.

There were entry/exit procedures for the production areas in place. Personnel had to change clothing suitable to the work environment defined. Personnel gowning procedure was described in a SOP including

wet chemistry and controlled areas. External contractor was used for laundry and repairing services. The controlled area gowns were cleaned twice a week.

3. Buildings and facilities

The manufacturing facility was located at Dhothigudem Village, Pochampally, Mandal, Nalgonda District of around 45 kilometers from Uppal, Hyderabad. The eastern and western sides were agricultural areas. On Southern and Northern side of the facility other pharmaceutical manufacturing companies were located. The site area was around 6.3 acres (25,490 sqm.). All the buildings were constructed of brick / RCC fabrication. The age of the buildings was 2 to 9 years.

Design and construction
The buildings and facilities inspected were designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture.

The facility layouts were available. Floor layout of Block 4 and AHU layout of the same area were checked.

All the production blocks were not dedicated to poducts. The final purification, drying and packaging of Linezolid took place in a controlled Grade D clean area.

HVAC systems
HVAC systems provided filtered air to cleanrooms used for final stages of processing to meet requirements for a Grade D environment. There was a procedure for qalification of clean rooms. Specifications included pressure differentials between Grade D clean area and other production area of at least 1.5mmwc and at least 20 air changes per hour. The HVAC is requalified annually. The AHU which supplied air to module II block 4 was checked and considered acceptable generally.

Water system
Purified water was used in the wet chemistry and powder processing areas. The primary treatment water was prepared by using underground water. Purified Water was tested according to USP / Ph.Eur requirment. Purified water system layout was available. The water generation storage and distribution system was sanitized at regular intervals of time as per the procedure given in a SOP.

Conductivity, pressure, flow, temperature was monitored on line of the purified water szstem and off-line sampling user points as defined in the schedule. The trending of QC data for month July (approved on 12/08/16) and the recent test data of user point 014 were reviewed.

Containment
Production block1, 2 &4 used for the production of Linezolid was not dedicated to this API. Other substances for pharmaceutical use were produced in the same plant. No highly sensitising or highly toxic APIs were produced in the blocks as stated by the company.

Lighting
Lighting was considered to be adequate in all areas visited during the inspection.

4. Process equipment

Design and construction
Manufacturing equipment was designed for the operation and in view with the area and class in which they are installed. All the critical equipment parts, which are coming in contact with the product, are made easily cleanable. List of manufacturing equipment are enclosed in the SMF and the validation master plan.

Equipment maintenance and cleaning
The detailed equipment preventive maintenance program (including monthly, quarterly, half-yearly, annual) and corresponding SOPs were in place. Head of engineering and utility was responsible for maintenance and repair of production and utility equipment. General maintenance of premises was carried out by the engineering and maintenance department but in certain cases outside contractor was also used. Equipment maintenance reports were available.

Critical process equipment and utility systems were subjected to formal qualification with Design Qualification, Installation Qualification, Operational Qualification and Performance Qualification. Re-validation was due in specified intervals. The validation and qualification schedule was made part of the VMP and available for year 2016.

The maintenance planner, protocol and records of a centrifuge were available and reviewed.
The qualification records of a centrifuge including URS, DQ, IQ, OQ and PQ were reviewed.

Manufacturing areas and equipment were cleaned and disinfected according to batch-to-batch and product change-over procedures using purified water, organic solvents and disinfectants as appropriate.
The list of solvents defined product-wise was available. The cleaning procedure of a centrifuge was described in a written procedure.

Calibration
The calibration of instruments/equipment was according to an annual schedule. A centrifuge reviewed was listed on the annual calibration planner 2016, and the last calibration records were available. Measuring equipment was required to be labelled with its calibration status and all examples viewed were within date.

Computerized systems
There was software “Empower 3” installed to network the HPLC and GC in the QC lab after last inspection. The access control, configuration, validation and operating procedure were reviewed.
Non-compliances observed during the inspection that was listed in the full report regarding computerized system were addressed by the manufacturer to an acceptable level.

5. Documentation and records

QA department was responsible for the preparation, revision and distribution of quality related documents according to a SOP. The documents (e.g. BPCRs, formats, procedures/policies) were prepared by the concerned departments then reviewed, approved, distributed, archived by the QA. The documentation

system was paper-based but several QC records (e.g. chromatograms) were handled and stored in electronic form. There were department-wise indices available for the issued SOPs (QA/ QC/ Prod/ DevAnal/ WH/ Eng/ IT/ Microbi/ HR).

The manufacturing activities were recorded in batch production and control records issued by the QA department.
There were two types of batch numbers in place: "in-house" and "commercial" batch numbers. In-house batch numbers were generated product-wise, recorded in a logbook and indicated on the BPRs.

6. Materials management

General controls
Handling of materials and products such as receipt, quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution were defined in SOPs and records were maintained. Raw materials were dispensed by warehouse personnel in the dispensing room and recorded in the issuance slip. The dispensing and stocking of the materials was recorded in Material Issue Records (loose card) and in the weekly updated "Raw Material Stock Details" document. Based on the raw material analysis request the QC issues an AR (analytical report) number, sample, test the material and the QC head/Deputy QA head decides on the release or rejection.
Finished API products were transferred from the production to the finished product warehouse after release. Status labeling was carried out manually.

Receipt and quarantine
Materials upon receipt were kept in staging area in the warehouse then transferred to the appropriate storage locations. Solid raw material and packaging materials were received in Warehouse 2 and Liquid materials in drum in Warehouse 1 and tank farm for bulk solvent according to a SOP. All the materials used and produced at the site had unique item codes. The receipt of the material was recorded in a material receiving checklist and entered into an inward register.

Sampling and testing of incoming production materials
The QC department was responsible for sampling of raw materials, intermediates, APIs. The sampling procedures and records contained amongst the number of containers to be sampled, amount sample. The in-process sampling was carried out by production personnel. The containers sampled were labelled with a sampled label.

Vendor approval
All manufacturers of key raw materials, general raw materials and packing materials were approved through vendor approval procedure. The vendor approval was carried out as per a SOP and based on amongst questionnaire, quality specification and performance testing of the material audit as appropriate. The vendors were approved by QA head or deputy.
A selected vendor qualification records were reviewed. The vendor was first used in 2012 for development materials, qualified on 2013 based on questionnaire, synthesis chart, catalyst and RM list, solvent usage, impurity profile, specifications and CoAs, MSDs.

Storage

In Warehouse 1 There were designated areas for storage of liquids (in drums), hazardous and fuming materials, raw materials, receiving area, de-dusting area. Besides the storage areas there were sampling booth, rejected area and dispensing booth located at the warehouse.
Tank farm was available for storage bulk solvents.
The Warehouse 2 was for storage of solid raw including materials, intermediates and finished with separated area for quarantine and approved materials, rooms for de-dusting, sampling and dispensing storage of rejected materials in room temperature. Intermediates, packing materials and finished products were stored in the first floor.

7. Production and in-process controls

Production operations
Production of Linezolid took place in the Production block-1, 2 and 4. There was no production in operation for Linezolid API at the time of inspection.

The production operations involved organic reactions followed by unit operations like filtration, centrifugation, distillation, drying, milling, shifting, packing.

The intermediates and active pharmaceutical ingredients were packed into food grade polythene bags.
Only one product was processed within the controlled areas (modules) at the same time.

In-process sampling and controls
In-process sampling was performed at defined stages during processing. In-process samples were tested in the QC laboratory.

Blending batches of intermediates or APIs
Blending operation was not used for WHO pre-qualified products as committed in the DMF.
Tailing materials were handled according to a written procedure.

8. Packaging and identification labelling of APIs and intermediates

The labelling of the materials was a function shared between the QA (status labelling), QC (sampling), Warehouse (material labels) and Production (labelling of intermediates) departments.

9. Storage and distribution

Warehousing procedures
There were documented procedures for the receipt, quarantine, sampling and release of materials. Computerized systems were not used for material control and a manual bin-card system was used.

Distribution procedures
The APIs release and labelling procedures were inspected and discussed. Non-compliances observed during the inspection that was listed in the full report regarding product release were addressed by the manufacturer to an acceptable level.

10. Laboratory controls

General controls
The company's QC lab and R&D lab were sit in the same building. The QC lab was testing of raw material, intermediate, in-process, API, cleaning validation and water samples. Besides physicichemical testing, there was a microbiology laboratory operated for testing microbial limits of purified water and APIs.

QC department was also responsible for conducting the stability and hold-time study analysis and for the calibration and qualification of QC instruments / equipment.

The quality control facilities consisted of HPLC room, GC/spectrophotometry room, stability chamber room, wet laboratory, microbiology laboratory, wash area, sample receiving area, TOC room, particle size analyzers, balance room. The main analytical equipment: HPLC, HS/GC, UV-Visible spectrophotometer, FT-IR spectrophotometer, potentiometer, pH meter, digital melting point apparatus, Karl Fischer titrator, balances, stability chambers. The chromatographs were connected into a network operated by Empower 3 software.

Testing of intermediates and APIs
The quality attributes and the corresponding test methods were summarized in quality specifications and standard test procedures (STP). Specification and STPs of Linezoid related KSM, intermediate and finished API were checked.

Testing samples entering the QC laboratories (including microbiology) were recorded in inward registers. Analytical equipment had instrument logbooks including the main data of usage. The break-down of a TOC instrument was reflected in the logbook.

Microbiological testing
The microbiology laboratory was part of QC Laboratory. The media preparation procedure and records were spot checked.

Handling of out of specification (OOS) results
The OOS results were investigated according to a SOP. OOS register of 2015 and 2016 as well as Linezolid related OOS investigation records were reviewed.

Validation of analytical method
The analytical test methods of APIs were validated ar required by the validation master plan. The documents of analytical method validation for related substances of Linezolid were available for review.
The analytical equipment were qualified after installation then regularly maintained and calibrated.
The calibration of HPLCs was due in every 3 months according to a SOP.
The qualification and calibration records of a HPLC were available and checked.

Stability monitoring of APIs
A SOP described the stability policy including the on-going stability testing and the hold-time stability testing of intermediates. The expiry/retest period of the materials was defined based on stability data and listed in a document. The stability chambers were located in the QC laboratory. Linezolid samples for

stability study were stored under the different conditions according to requirement.The handling/management/stocking of stability samples was paper based (Stability Chamber Log).

Data Integrity of chromatography systems

The company has established a chromatography data network and begun to establish controls since March 2015. Chromatographic test raw data were managed electronically. The audit trails were reviewed monthly and was recorded in a logbook. The user administration was based on a formal request for user which was approved according to a SOP. The list of user together with the user groups and privileges was documented and in-line with the user list of the system.

The system audit trail was appropriate to trace back the removal of two administrators and an analyst.

STP for linezolid and some test results of the stability batches were checked in a HPLC.

11. Validation

Validation policy

The company's overall validation policy was adequately described in a documented VMP which described validation requirements including frequency of re-validation.

Qualification

Major equipment was qualified according to documented protocols and records were maintained. Requalification of the equipment was 5 years maximum.

Process validation programme

The company's validation programme was scheduled annually. An annual validation schedule of 2016 was available including PV, equipment qualification and analytical validation.

Process validation was performed according to a SOP. Individual process validation protocols were prepared before the validation activities referring the process equipment, batch numbers (at least three consecutive validation batches), batch manufacturing records, critical process parameters, specifications, test methods.

Process validation documents of Linezolid APIMF 286 and APIMF 255 were reviewed at the time of inspection.

Cleaning validation

Cleaning validation was performed according to a SOP. Equipment cleaning types included batch to batch, periodical, stage changeover cleaning with the same product and product change over.

Cleaning validation protocol and report for Cleaning of equipment including reactor, centrifuge and tray drayer were reviewed. 10 ppm was used as acceptance criteria for residues.

Computerized system validation

A chromatography data network has been established with server and Empower 3 software. The computerized system validation was reviewed. The following documents were reviewed.

- SOP for handling Empower 3 software
- Protocol for the implementation of Empower 3 Server for HPLC and GC instruments laying in QC
- SOP on Good Chromatographic Techniques
- SOP for Audit trail review

Non-compliances observed during the inspection that was listed in the full report regarding computerized system validation were addressed by the manufacturer to an acceptable level.

12. Change control (CC)

Change control was managed according to a SOP. Changes were classified into critical and non-critical, as well as temporary and permanent change. Annual review was not required in the procedure. Annual review of CC was not performed.

The changes were formally investigated and approved by the QA head. The investigation records of change on the BPR and stability protocol preparation for a reprocessed batch were reviewed and found generally acceptable.

13. Rejection and re-use of materials

Reprocessing and reworking

Reprocessing and rework was undertaken in consultation with R&D if approved by QA as per a SOP. No rework was recorded since the last WHO inspection. There were a number of reprocessing performed in 2015 and 2016 according to reprocess log. Reprocess records of a Linezolid batch were reviewed. The batch was released. The stability program of the batch was performed.

Recovery of materials and solvents

There was no recovered solvent used for the WHO product as committed in the dossier.

14. Complaints and recalls

Market complaints were handled according to a SOP. Complaints were classified into critical, major and minor. Complaint registers was maintained.

Recall procedures remained the same and no recall was recorded since last inspection.

15. Contract manufacturers (including laboratories)

No contract manufacturing is being done. There are analytical test of RM/IM/API/PM contracted out. The contract partners providing analytical testing were qualified according to a SOP. The qualification records of the laboratory providing XRD/DSC/potentiometry/elemental analysis were reviewed. The quality agreement and site audit report were available for inspection.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned. Linezolid (APIMF 255) and Linezolid (APIMF 286) manufactured at Optimus Drugs Private Limited located at Survey Number-239 & 240, Dothigudem (Village), Pochampally (Mandal), Nalgonda (Dist), Telangana, India, PIN: 508 284 were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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

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

PART 4

List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   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/

3. 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
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

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

5. 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
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

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

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

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
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
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
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
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
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
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
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
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 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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