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Prequalification Team Inspection services

WHO PUBLIC INSPECTION REPORT (WHOPIR) Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Lupin Limited, Unit-1, Pithampur**
Corporate address of manufacturer	3rd floor, Kalpataru Inspire Off. Western Express Highway Santacruz (East) Mumbai - 400 055 India
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Unit 1, Plot No 2, Special Economic Zone, Phase II SEZ, Pithampur, District Dhar, Madhya Pradesh, 454 775, India DUNS: 65-058-2310 GPS: Latitude, longitude: 22.614546, 75.652537
Synthetic unit /Block/ Workshop	Unit 1 (API-1 and API-2)
Inspection details	
Dates of inspection	18-22 March 2019
Type of inspection	Initial GMP inspection
Introduction	
Brief description of the manufacturing activities	Lupin Limited, Pithampur (Unit 1) is located at Plot No. M-2 & M-2-A, Special Economic Zone Phase, II, Misc. Zone, Apparel Park, Pithampur-454 775, (Distt. Dhar), M.P., India. Unit-1 is involved in the manufacturing of API & Formulations. The API section has three API plants: o API-1 (640.78 square meters), o API-2 (6141.12 square meters) and o API-3 (1286.77 square meters).

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	The API manufacturing facility of Unit-1 is engaged in the manufacturing of Hormonal & Steroids product. From the opening meeting presentation, the plant capacity was noted as follows: o API-1: 5 to 10 Kg/Month o API-2: 25 to 120 Kg/Month o API-3: 0.25 to 15.0 Kg/Month
General information about the company and site	Lupin Limited was founded in the year 1968. It has a presence in Pharmaceutical Formulations, Bulk Drugs, Herbals & Biotechnology based products. The specialties include Anti tubercular drugs, Cephalosporin & Cardiovascular drugs. The company has 18 manufacturing sites across the globe (12 in India, 3 in Japan, 1 in Mexico, 1 in Brazil & 1 in the USA, out of which 6 are API sites and rest of them are formulation sites)
History	This was the first WHO PQ inspection of Lupin's Unit-1 facility. *The API manufacturing facility was licensed by the Food and Drugs Administration (FDA), Madhya Pradesh and valid to 30 June 2020*
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	**Document Review included but was not limited to:** o Organization Chart o Responsibilities of the quality units and production o Job descriptions for key personnel o Personnel training and hygiene o Product Quality Review o Quality Risk Management o Complaints and Recalls o Deviation control and change control o CAPA procedure o OOS and investigation o Self-inspection and vendor qualification o Validation and qualification o Data integrity o Sampling, testing, and release of materials and products o Batch processing and analytical records o Materials management system o Purified water system o Heating ventilation and air-conditioning system (HVAC) **Site areas visited:** o API-1 and API-2 o Warehouse o Purified water system o HVAC

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Restrictions	None
Out of scope	APIs out of WHO scope including API-3 and formulation manufacturing
WHO APIs covered by the inspection	Norethisterone (INN) / Norethindrone (USP) APIMF372-0
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system

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PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

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

1. Quality management

A formal documented system of quality assurance was established, with procedures covering all expected key quality elements being in place. QA and QC departments were independent of production. Operations were specified in written form and GMP requirements were essentially being met. Procedures were in place for notifying responsible management of regulatory inspections, serious GMP deficiencies, product defects, and related actions. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Product and processes were monitored, and these results considered during batch release. Regular monitoring and reviews of the quality of APIs were being conducted according to documented schedules and procedures.

The quality management and quality control functions were supported by IT software:

Handling through Quality Assurance Management System (QAMS)

- Deviation
- Change Procedure
- Market Complaints
- CAPA (Corrective action and Preventive action)

Manual Handling

- OOS (Out of Specification)
- OOT (Out of Trend)
- APQR (Annual Product Quality Review)
- Failure / Nonconformance investigation

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Systems handled through SAP
- Batch production records preparation, review, approval, and issuance.
- Vendor qualification
- Stability study program
- Calibration and Preventive maintenance of production equipment and laboratory instruments
- Maintenance notification

Document control through software (OMNIDOCS)

Electronic Log book for analytical instruments and production equipment

Quality risk management/QRM procedure was discussed. Risk assessment was performed both prospectively (as part of the changes introduced onsite) and retrospectively (incidents, deviations, complaints, recalls, etc). The risk assessment was performed by a cross functional team. The proactive/prospective risk assessment was performed using HAZOP, FMEA, HACCP, PHA, and risk ranking whereas for retrospective risk assessment, investigational approaches such as fish bone analysis, 5 WHY, etc were applied. The risk priority number (RPN) was calculated based on the likelihood, detectability, and severity of the risk. A scale of 1 to 5 was used and risks were classified into High Risk (65-125), Medium Risk (9-64) and Low Risk (1-8). In general, the QRM procedure was found adequate.

Management review of quality metrics procedure was reviewed. The quality metrics at the site level was reviewed once per month whereas quality council meeting was also conducted monthly with the senior management through webinar or skype. Minutes of the last site meeting was briefly reviewed which was attended by representatives from all departments. The site meeting included discussion on the testing summary, timeliness metrics, market complaints, recall, returned goods, batch failure, change controls, deviations, out of specification (OOS), conditional release of raw materials, packaging materials, finished products, regulatory audit, batch reprocessing, out of trending (OOT) and key starting materials.

Product quality review (PQR)
In accordance with SOP, "Annual Product Review of drug substances and saleable intermediates" was performed. The PQR included the review of manufacturing process data, critical process parameters, batch yields, analytical test results, recalls, deviations, change controls, complaints, CAPA, returns, stability data, qualification, and requalification status, batch rejections, reprocessed /reworked/repacked batches, utilities, water monitoring, environmental monitoring, post marketing commitment, key raw materials, primary packaging materials, technical agreements, trending of finished product results, in process and intermediates. The Head of QA was responsible for approving of PQR.

Deviation Management
As stated in the SOP, "Handling of deviation" a deviation handling system for evaluation of deviations were in place and adhered to during manufacturing, packaging, storage and testing activities. As per the SOP, all employees were responsible for identifying and reporting of deviations. Deviations were reviewed by various specialists (from various departments) and finally approved by the Head of QA. The deviation process was described in detail in the SOP. In 2018, 5 deviations, concerning Norethindrone USP, were observed. The deviation proceeded in compliance with the SOP.

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Corrective actions and preventive actions (CAPA)
The CAPAs were proceeded according to SOP, "Corrective action and preventive action". The procedure was appropriately described. The CAPAs were reviewed by various specialists (from various departments) and approved by the Head of QA.

Out of trending (OOT)
The SOP "Trend analysis of quality parameters and out of trend investigation" was applicable to commercial production and stability study results. The SOP was intended to detect any out of trend results and identify assignable causes to take appropriate corrective and preventive actions. As stated in the SOP, "in cases where OOT results have been confirmed, an impact assessment on the product quality shall be done (for example impact on same or other batches where the material was used). Such assessment shall be documented and shall be part of the batch investigation report.

Vendor qualification
Qualification of vendors was carried out based on the "Vendor qualification" procedure. Qualification of

Training
According to SOP, "Training of personnel" the company had a structured training program which covered all employees. The following types of training were conducted for employees: cGMP training, job-related training, and self-develop training. The manager /supervisor was responsible for notifying employee group training needed and ensuring its periodic review (once a year), ensuring that the employees participated in internal and external training courses as described in the training plan. Software based system was in place for managing all the training related activities.

The deficiencies raised from this section have been satisfactorily addressed through submission of CAPAs, and the same shall be verified during routine inspections.

2. Personnel

Personnel met during the inspection appeared to have knowledge of GMP principles and showed that they received initial and continuing training, including hygiene instructions, relevant to their responsibilities. Measures were taken to prevent unauthorized people from entering production and QC areas and appeared to be effective. An organization chart was available.

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The manpower of the company dedicated to Unit-1 API was as follows:

No.	Department	No. of employees
1.	Quality Assurance	5
2.	Quality Control	17
3.	API-1 (production – PR1)	18
4.	API-2 (production – PR5)	31
5.	API-3 (production – PR6)	19
6.	Validation	4
7.	Warehouse and Purchase	12
8.	Engineering	35
9.	HR and Administration	17
10.	Contract basis	10
	Total	168

The deficiencies raised from this section have been satisfactorily addressed through submission of CAPAs, and the same shall be verified during routine inspections.

3. Buildings and facilities

The manufacturing facilities were not API dedicated.

The API manufacturing facility has separate raw material and packaging material storage area and finished goods warehouse. Adequate lighting and ventilation are provided in all areas.

The facility is designed to handle sensitizing materials such as Hormonal /Steroidal /Nonsteroidal drug substance. The HVAC system provided filtered air to the Grade D cleanrooms. The manufacturing area was designed with HEPA filter in supply and return air ducts. The manufacturing area was temperature controlled & differential pressure maintained between the room as per the requirement to control the cross contamination. The temperature in the process area was controlled at not more than 25°C. Adequate ventilation, air filtration, and exhaust systems were provided.

Lighting in the areas visited during the inspection was considered adequate.

The flow of materials and personnel through the facilities were designed to prevent mix-up and cross contamination.

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Separate purified water (PW) systems were located in the API-1 and API-2 plant. The PW system located in API-2 was briefly inspected. In general, the water system was designed, installed, commissioned, qualified and maintained to ensure the reliable production of water of an appropriate quality. The PW was produced by ion exchange and double pass reverse osmosis. The PW was distributed to API-2 and API-3 plants. The water system was not equipped with electro deionization (EDI). In general, the water system appeared to be appropriately maintained.

Purified water met the specification requirements of Process water used for manufacturing & final rinsing of equipment /component.

Inspected workshops and facilities were maintained at an acceptable level

4. Process equipment

Equipment used in the manufacture of Norethindrone appeared to be of appropriate design and size for its intended use. In general cleaning and maintenance appeared satisfactory.

Process equipment in API-1 and API-2 plants were not API dedicated and both plants manufacture intermediates and finished APIs.

Materials of product contact were suitable. Reactor systems and utilities were installed to allow reflux, distillation, and cooling required to make the APIs of interest.

Tools and equipment were uniquely identified and status labels were generally used. Similarly measuring equipment were labelled including calibration status. In general, they were maintained according to written procedures and a plan for preventive maintenance was available.

Computerized systems were not used for production control.

A computerized system was used in the QC lab for HPLC and GC networking.

The deficiencies raised from this section have been satisfactorily addressed through submission of CAPAs, and the same shall be verified during routine inspections.

5. Documentation and records

Documentation system was generally well established. Procedures on creating SOPs and on control of quality documents and records were available. The issuance, revision, superseding and withdrawal of documents were controlled. Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures. Specifications were established for raw materials, intermediates, and APIs. BMRs were retained for each batch processed. Batches were numbered according to a written procedure for product batch numbering.

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6. Materials management

The API warehouse layout located on the ground floor was discussed. It was noted that separate areas were provided for incoming starting materials, carbon, solvents and acids. Control temperature condition was provided below 25ºC for the incoming materials.

The warehouse has one sampling and one dispensing area equipped with separate material airlock (MAL) and personnel airlock (PAL). Sampling and dispensing were carried out under reverse laminar airflow (RLAF). Dispensing of liquids was carried out in an area equipped with an exhaust system. Inside the controlled room, rejected materials were stored and identified using red rope. The finished goods store was maintained at 25ºC wherein Levonorgestrel and Norgestrel USP were stored. The Data Acquisition System (DAS) was used for displaying temperature within the warehouse area. Approved vendor list was maintained using the SAP system.

The deficiencies raised from this section have been satisfactorily addressed through submission of CAPAs, and the same shall be verified during routine inspections.

7. Production and in-process controls

Manufacturing of drug substance intermediates / APIs was as follows:

Facility	Products manufactured
API-1	Hormonal & Steroids product (Small Facility)
API-2	Hormonal & Steroids product (Large Facility)
API-3	Prostaglandins & Other API Products

The API-1 is a small-scale facility for hormones whereas API-2 is a large-scale facility. It was indicated that API-3 was not used for the manufacturing of the sex hormone Norethindrone.

The API-1 plant layout was reviewed. The first-floor housed air handling units whereas ground floor has reactors and utilities. Processing room number 4, 5, 6, 7, intermediate storage room and packing room were classified as ISO 8. The API-2 ground floor layout was reviewed. The API-2 has four floors (ground, first, second and mezzanine for service area) and each floor has areas for intermediates as well as for final processing. The final processing area (vacuum tray dryer, rota vapour, centrifuge, packing, and finished product material storage area) was classified as ISO 8. It was noted that powered air purifying respirator (PAPR) and isolators were used before charging materials for the next process.

The production areas under the scope of this inspection were inspected and generally found to be of a suitable standard, clean and logically organized to suit their intended purpose.

At the time of the inspector's visit, no production activity was being carried out.

The deficiencies raised from this section have been satisfactorily addressed through submission of CAPAs, and the same shall be verified during routine inspections.

8. Packaging and identification labelling of APIs and intermediates

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The final finished API was packed in the packing area equipped with balance and was stored in the packing material storage area. The packed material was moved to finished goods warehouse through pass-box. The area was maintained at 25ºC and temperature was displayed.

Packaging and labelling were not in operation at the time of inspection.

9. Storage and distribution

Finished APIs were stored in a designated warehouse and held until released by the QA.

APIs and intermediates were released for distribution following release by the QA.

The deficiencies raised from this section have been satisfactorily addressed through submission of CAPAs, and the same shall be verified during routine inspections.

10. Laboratory controls

The laboratory was equipped with sophisticated equipment and instruments and was manned by 117 personnel. It was indicated by the laboratory that 25 personnel were responsible for the testing of APIs. Senior manager QC was overall responsible for the laboratory operation who in turn reported to General Manager QA.

The laboratory was biometric access control. The senior manager QC was supported by four QC managers (responsible for APIs, GLP, microbiology, formulation, and stability). In addition, Rajesh Jain (lab QA manager) was responsible for the investigation and review of analytical reports and directly report to Head QA.

The premises were generally of an acceptable standard and well equipped. Documents were organized in an appropriate manner and retrieval was achieved in a timely manner.

Microbiological laboratory

The microbiological laboratory was in the QC area. All microbiological tests of APIs, process water, purified water and all activities related to microbiological monitoring performed in this area. All production samples were kept in a dedicated, lockable cupboard. Access to the samples was controlled and registered. Critical activities were performed in the clean room under the LAF. The incubation room was equipped with 6 incubators (various condition of temperature and humidity depending on tests). Furthermore, the laboratory was equipped with 2 autoclaves. One of them was in the clean area and was dedicated for sterilization of glassware, media end equipment. The second one was in a separated, unclassified room and was designated to the destruction of microorganisms after tests.

Microbiological monitoring of air in the production area was performed once a month. The results from 2018 met acceptance criteria. All media were prepared and tested (growth promotion tests) in the laboratory.

Purified Water (PW)

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Purified water was tested according to the specification of purified water USP/Ph EUR, (acceptance criteria: pH 5.0 -7.0, TOC 500 ppb, conductivity 1.3 µm/cm in 25ºC, heavy metals NMD 1 ppm, nitrate NMT 0.2ppm, total microbial counts NMD 100 CFU/ml, absent in 100 ml Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Salmonella.) There were 63 user sampling points of PW in the API production area. Every day 6-10 samples were taken for testing.

Stability studies

Specification for Norethindrone USP was applicable for commercial batches, as well as for stability studies (long term, intermediate and accelerated). As stated in the specification, the microbiological examination had to be performed only on the first three commercial batches and subsequently on every 10^{th} batch or annually whichever is soonest. It was noted from the specification that microbiological examination was performed for monitoring purposes only and not as release criteria. The specification was in compliance with the dossier. The frequency of microbiological tests for stability studies was indicated in the appropriate SOP.

The deficiencies raised from this section have been satisfactorily addressed through submission of CAPAs, and the same shall be verified during routine inspections.

11. Validation

A site level validation master plan (API facility) was in place. The CQA procedures are the guidance documents for the implementation of VMP.

Process validation report of Norethindrone USP was briefly discussed. Three batches were taken for the validation study using key starting material. Process performance qualification (PPQ) report of Norethindrone USP was briefly discussed.

Cleaning validation master plan for API manufacturing facilities was discussed. The plan stated that on completion of cleaning verification studies, a cleaning validation study will be undertaken to demonstrate three consecutive successful cleaning cycles. The master plan was last prepared in June 2012 and had not been updated since then. Also, cleaning validation acceptance limit was still based on the dose criteria (0.01 dose of any product i.e. MACO using a swab and rinse sampling) and general limit of 10ppm. The plan stated that if the use of toxicological data leads to unacceptable high MACO, follow 10ppm limit.

The deficiencies raised from this section have been satisfactorily addressed through submission of CAPAs, and the same shall be verified during routine inspections.

12. Change control

According to the SOP, there was a change control system which provided an assessment process to evaluate planned changes to determine what level of testing, validation, and documentation was required to justify changes. All changes were categorized as major or minor. Changes were reviewed by various specialists (from various departments) and finally were approved by Head of QA.

In general, change controls were handled in accordance with company's procedure.

13. Rejection and re-use of materials

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Reprocess and rework of drug substances/ intermediates was discussed. The QAMS was used for the handling of reprocessing and reworking of the drug substances and intermediates. In case of non-availability of QAMS, reprocessing shall be handled manually using logbook. Reprocessing of batches performed the first time shall be released only after completion of 3 months accelerated stability study. A unique number was assigned to reprocessing batches. Reworking was handled in a similar way. It was indicated that reworking for Norethindrone was not performed.

It was indicated by the company that solvents are not recovered and not used in the manufacturing of Norethindrone.

14. Complaints and recalls

Complaints
The SOP, "Handling of market complaints about drug substances (APIs) and intermediates" was applicable to all drug substances and saleable intermediates manufactured and marketed by the company. All activities concerning complaints were described in detail. The Head of QA was responsible for final decisions concerning the complaint. There were not any complaints concerning Norethindrone USP in 2018.

Recall
Written procedure covering voluntary recall and recall requested by the drug control authorities were reviewed. The recall process was described in detail. As stated in SOP the decision for recall was taken by the Recall committee. The regulatory Authorities are informed about the recall. There were not any recall concerning Norethindrone USP in 2018.

15. Contract manufacturers (including laboratories)

It was confirmed by the company that contract manufacturing has not been applied to any stages of Norethindrone manufacturing.

Part 3	**Conclusion – 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, ***Lupin Limited, Unit-1***located at ***Special Economic Zone, Phase-II SEZ, Pithampur, District Dhar, Madhya Pradesh, India*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

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

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

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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. ***Short name: WHO GMP for APIs or WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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

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

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

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. ***Short name: WHO HVAC Guidelines*** *or* ***WHO TRS No. 1010, Annex 8***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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