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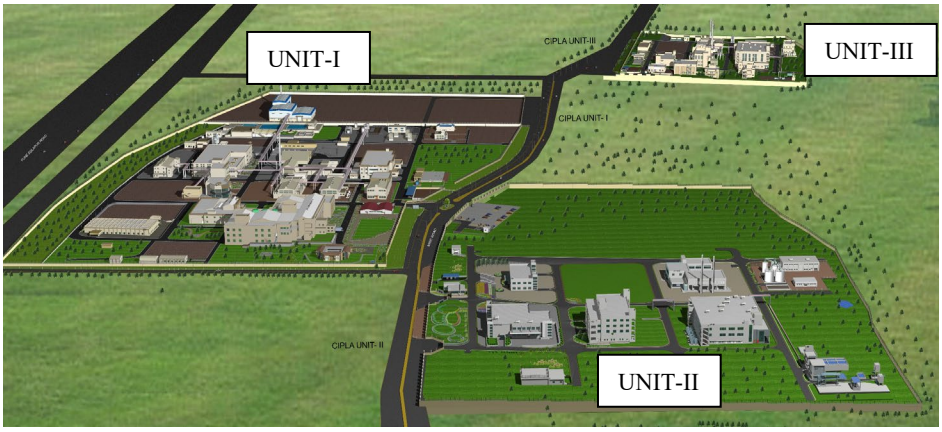
Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	General information
Manufacturers details	
Name of manufacturer	**Cipla Ltd**
Corporate address of manufacturer	Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai – 400 013, India. Phone: + 91 22 24826000 *Fax: +91 22 24826120*
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Plot D-7 (Unit1), MIDC Industrial Area, Kurkumbh Village, Taluka-Daund, Pune District, Maharashtra, 413 802, India D-U-N-S number of the site 917066446
Unit / block / workshop number	Unit-I (Pharma 1 & Pharma 2)
Inspection details	
Dates of inspection	15-19 April 2019
Type of inspection	Special GMP inspection
Introduction	
Brief description of the manufacturing activities	The pharmaceutical manufacturing activities at Kurkumbh were licensed by the Food and Drug Administration, Maharashtra State, India. The site is located in MIDC Industrial Area, 250 km from Mumbai and 70 km from Pune (near to Pune-Solapur Highway), accessible by road and rail (Daund Station). The aerial view of the site and its three Units is shown below: 

Unit-I (with built-up area 64,925m^2)

Block	Manufacturing Activity
Pharma I	Tablets, hard gelatin capsules, powders, pellets, Granules,
Pharma II	Soft gelatin capsule, oral paste
BD I	Multiproduct API
BD II	Multiproduct API
BD III	Multiproduct API
BD IV	Multiproduct API (respiratory corticosteroids)
BD V	Multiproduct API

Unit-II (with built-up area 28,264m^2)

Block	Manufacturing Activity
API I	Multiproduct API
API II	Multiproduct API

Unit-III (with built-up area 22,895m^2)

Block	Manufacturing Activity
BD I	Multiproduct API
BD II	Multiproduct API (Hormone)
BD III	Multiproduct API
BD IV	Multiproduct API

All the APIs and the FPPs manufactured on site are classified as non-sterile dosage forms.

General information about the company and site	Cipla Ltd is a public limited company established in 1935. It manufactures and markets a wide range of pharmaceutical formulations and Active pharmaceutical ingredients (APIs). The Corporate headquarter including corporate QA and Research & Development is located at Mumbai. Senior personnel are available there for providing support to the manufacturing units in the areas of technology, Integrated Product development (IPD), Manufacturing, Quality Control, Quality Assurance and Regulatory Affairs.
History	The FPP site located at Kurkumbh has been regularly inspected by the WHO PQ inspection team. The site was last inspected by WHO in March 2016. The site has also been inspected by several regulatory authorities, e.g. the USFDA in March 2019.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The inspection involved spot checks of the quality assurance system and investigations focused on the operations relating to the manufacture, quality control and quality assurance of the eight FPPs that are under WHO PQ, manufactured by Cipla Kurkumbh in Unit I.

	The inspection team also investigated corrective actions implemented by the site following the issue of the USFDA Form 483 in March 2019
Restrictions	No r
Out of scope	None
WHO products covered by the inspection	HA056 (Ciprofloxacin (hydrochloride) Tablet, Film-coated 100mg) HA057 (Ciprofloxacin (hydrochloride) Tablet, Film-coated 250mg) HA058 (Ciprofloxacin (hydrochloride) Tablet, Film-coated 500mg) HA059 (Ciprofloxacin (hydrochloride) Tablet, Film-coated 750mg) HA208 (Fluconazole Capsules, hard 150mg) HA209 (Fluconazole Capsules, hard 200mg) MA124 (Artesunate Capsule, Soft, Rectal 100mg) MA064 (Artemether/Lumefantrine Tablet 20mg/120mg)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch Packing production record
CC	Change control
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
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae

MFT	Media fill Test
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
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. Pharmaceutical quality system

The quality management system (QMS) of Cipla is centrally (corporate level) driven in order to harmonize systems but managed at site level.

A formal documented system of quality assurance was established, with procedures covering all expected key quality elements being in place. The QA and QC departments were independent of technical (production) operations. Operations were specified in the written form. 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 satisfactory. 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.

In general, the Pharmaceutical Quality System of the FPP Unit and the three API Units was the same as it was driven by the same Corporate and site-level procedures.

Annual product quality review

Annual product quality reviews were conducted in accordance with procedure (1035-G-0016 version 9.0 dated 29th March 2019).

Deviation management

The use TrackWise application for the management of deviations was initiated in 7th July 2017. Prior to that the software called Smart Solve Pilgrim was used. Unplanned deviations were reviewed and noted that adequate investigation was performed to find out root cause.

Change control

Review of CIPDOX software showed the following:

Year	Total change requests	minor	moderate	Total major	Major closed
2016	1330	1005	296	29	18
2017	1170	924	232	11	5
2018	1251	915	231	4	1
2019 (up to 16 April)	4	185	75	4	

Quality risk management

Risk management study (FMECA/1018/18/013/01) using FMECA dated 10/10/2018 was performed for equipment and process of Artesunate suppositories 100mg in the shared facility. This risk analysis was performed before the commercialization of Artesunate suppositories 100mg to assess product related potential risks and compare against the existing controls. In general, risk management study was found adequate.

Quality Management review

Quality management review (QMR) requirements were outlined in the Quality Manual. The QMR procedure was described in the SOP "Quality Management Review". The SOP "Management Review and escalation procedure" was also reviewed and noted that review was performed on monthly and quarterly basis.

2. Good manufacturing practices for pharmaceutical products

Refer to other sections covered in this report.

3. Sanitation and hygiene

Not inspected

4. Qualification and validation

Corporate SOP for calibration was in place. In addition, other calibration and verification SOPs were available for various equipment and instruments used by the facility. The annual calibration schedule for 2019 for Unit I was available and included instruments for yearly, six months, and every two years. Also reviewed for Unit I, Pharma II where the soft gelatin capsules under the WHO PQ were manufactured. It showed the schedules and records of those so far done for the temperature controller with sensor, thickness gauge, temperature indictor with sensor, temperature transmitter, Vernier caliper vacuum gauge, vacuum transmitter, wet & dry hygrometer, all of which were six monthly calibration.

Calibration schedule for the laboratory equipment was printed from the LIMS; had daily, monthly, quarterly, and half-yearly, and yearly calibration schedules, For the monthly balance calibration, the following tests were done: linearity, accuracy, repeatability and eccentricity. Raw data calibration sheet and LIMS report was for balance Mettler Toledo 1015_LAB1_I-276 was reviewed and found in order. Weigh box type E-2 box no. E-223 certificate no. TVCS 1608164 from True Value Calibration Services, also accredited to NABL, were used.

Preventive maintenance

SOP Preventive Maintenance (PM), Doc. No. EG-05 version 08, effective date 24/08/2018 for manufacturing equipment. PM was managed in SAP. Annual PM of the soft gelatin melter SG-140 was reviewed through SAP, planned in January and in April, i.e. quarterly frequency. The report of PM that was done in January was reviewed; a checklist in the SAP was used planned date 14/04/2019 and actual date was 8/04/2019 by engineering and checked by production.

Air handling units

AHU performance verification study done every year or earlier wherever change is done. The following tests are done: filter leakage test of H11/EU10 (0.3µ HEPA), number of air changes, CFM of inlet air across the filter, return air CFM, CFM through relief filter, CFM in duct (to test duct leakage), temp. and RH, pressure differential with the adjacent areas, airflow direction, particle count at rest and in operation, area recovery/clean-up period study, microbial count by settle plate and air sampling.

Environmental monitoring

Environmental temperature and RH electronic data were acquired by the SCADA system on a real-time and continuous basis, saved on the server and back-up done on daily basis. The system had alarm provision in case of out of limit of the temperature or RH excursions beyond one (1) minute. Daily alarm log sheet printout from the SCADA system were made by the engineering department and verified by user and QA.

Process validation

Process validation information was obtained for all WHO PQ products. Process validation report of Artesunate suppositories 100mg was reviewed and found adequate in general.

Analytical method validation

Analytical method validation report for dissolution of Artesunate Suppositories 100mg by HPLC was reviewed and found adequate in general.

5. Complaints

SOP "Handling of product complaints" applies to all APIs Units and to the Formulation unit. Scope drug substance and drug products manufactured for the local market as well as for the export market. Complaints managed in TrackWise software. Classified as critical (potentially life-threatening or could result is a serious health risk with serious medical consequences) and non-critical (could cause illness or mistreatment) complaints and categorised as technical complaints (related to quality parameters of the product) or medical (related to adverse event or reaction) complaints.

6. Product recalls

Not inspected.

7. Contract production, analysis and other activities

Not inspected.

8. Self-inspection, quality audits and suppliers' audits and approval

Not inspected.

9. Personnel

See notes under training.

10. Training

Training procedure was reviewed. The system was in place to provide induction training for the newly recruited personnel before the department and on the job training were provided. The newly recruited personnel is required to work under supervision or guidance before training evaluation (75%) was performed, competency matrix and certificate issued. Annual training schedule was prepared by the respective department heads based on discussion with staff and previous year's issues (deviations, human errors, data integrity, right first time) identified. Training schedule for 2019 for the various department was available. Various topics such as cGMP, APQR, trends of quality metrics and QMR, review of electronic data and audit trail, handling of rejected material, good documentation practices, environmental and water monitoring, line clearance, validation (process, cleaning, computerised), data integrity, nonconformance, investigation, root cause analysis & CAPA, qualification, RFT & human error, complaints & recalls and other. In general, the topics covered as part of the routine/refresher training appeared satisfactory.

11. Personal hygiene

Not inspected.

12. Premises

Not inspected.

13. Equipment

See more detail under section on qualification and validation.

14. Materials

Not inspected.

15. Documentation

The documentation system was supported by the following information systems applications:

a) TrackWise: implemented on 6th July 2017, used for deviations, complaints (log from CQA) and CAPA (related to non-conformance);
b) Cipdox: used for SOPs, specifications and change controls;
c) LIMS): Quality Control data management and printing of certificates of analysis. Full connectivity with pH meters, analytical balances, tap density; and functionality for OOS for the creation of OOS number and intimation through SAP, but rest of laboratory operations handled manually;
d) SAP: used for material inventory management system tracking, generation of master BMR and BPR and vendor management. Initiation of retesting was through SAP and then handled through LIMS.

16. Good practices in production

The soft gelatin capsule production areas were inspected. It was noted that production process of soft gelatine capsule was essentially manual in nature (loading and unloading of soft gelatine capsules to the printing machine). No evidence of contamination or cross-contamination was identified.

17. Good practices in quality control

Handling of out of specifications (OOS)

Trend analysis of OOS for 2016, 2017 and 2018 was reviewed.

Year	Total OOS	Confirmed / valid	Non-confirmed / invalid
2016	165	104	61
2017	114	76	38
2018	94	69	24 (1 open)
2019	33 (Jan-Mar)	22	7 (4 open)

Key initiatives were taken in January 2018 for reduction of invalid OOS/OOT in the laboratory. This was a common initiative for API and FPP products. This initiative was monitored in all four QC laboratories (Unit-I, API & FPP lab, Unit-II lab and Unit-III lab). It was noted that CAPAs were initiated to avoid analytical errors which led to invalid OOS. For example, supervision during analysis (senior analyst review junior's work), counselling & sharing of nonconformance, retraining, revalidation of the analyst, shifting of the analyst to other section, usage of intact septa, disciplinary action, revision of specification and General Analytical Methods. It was indicated by the laboratory that based on the invalid OOS reported by the analysts, appropriate actions (such as retraining, revalidation, disciplinary action and shifting of the analyst to other section) were taken.

Generation of trend limit and monitoring trend of quality attributes, procedure (1035-L-0062 version 4.0 effective date 29/01/2019) establishes trend limits and routine monitoring of trends of quality attributes generated from laboratory test results. Trend limit was determined based on the review of 25 batches data.

Microbiological monitoring of environmental, surfaces and personnel in the production area (1035-L-0086 version 6.0) was discussed. The procedure described monitoring of environment, surfaces and personnel area. Another procedure on the establishment of control 2 (alert) and high control 1 (action) (LIMS).

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, ***Cipla Ltd, Unit-1, Plot No. D-7, D-22, D-27, MIDC, Industrial Area, Taluka-Daund, Kurkumbh Village, District: Pune, Maharashtra 413 802, India*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

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

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

Part 4	List of WHO 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 GMP for APIs*** or ***TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/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 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

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 GPPQCL Guidelines or ***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

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

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

23. 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