World Health Organization

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**Prequalification Team Inspection services**
**WHO PUBLIC INSPECTION REPORT**
**of the FPP manufacturer**

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Company information | |
| Name of manufacturer | Oxalis Labs |
| Corporate address of manufacturer | 201 Mahavir Industrial Estate, Near Paper Box, off Mahakali Caves Road, Andheri(E), Mumbai 400093, India |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | Village Theda, P.O. Lodhimajra, Tehsil Baddi, Distt. Solan (H.P), India |
| Unit / block / workshop number | General Block including Rifampicin facilities |
| **Inspection details** | |
| Dates of inspection | 13 – 16 March 2018 |
| Type of inspection | Routine inspection |
| Representative from the National Regulatory Authority | Central Drugs Standard Control Organization was invited and attended this inspection |
| **Introduction** | |
| Brief summary of the manufacturing activities | The facility at village Theda was engaged in contract manufacturing of meter dose inhalers, semi-solid dosage forms for external use, topical solutions and oral solid dosage forms (soft gelatin capsules and tablets). |
| General information about the company and site | The company was established in 2012 and its headquarters are located in Mumbai. Oxalis provided exclusive contract manufacturing services to Macleods.<br>The site is located approximately 60 Km from Chandigarh airport. There are two (2) manufacturing blocks on site, namely the G (general) block and the M block. In the General block tablets, soft gelatin capsules, MDIs and rifampicin products were manufactured. Semisolids and liquids for external use were manufactured in M block. An extension to G Block was introduced in 2016. |
| History | This was the second WHO inspection. The last WHO inspection was carried out in April 2015.<br>The site was also inspected by Health and Family Welfare Department, Himachal Pradesh, India in March 2017 |

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| **Brief report of inspection activities undertaken** | |
| **Scope and limitations** | |
| Areas inspected | **Document reviewed including but not limited**<br>• Organization Chart<br>• Job descriptions for key personnel<br>• Personnel training and hygiene<br>• Product Quality Review<br>• Quality Risk Management<br>• Responsibilities of the quality units and production<br>• Complaints and Recalls<br>• Deviation control and change control<br>• CAPA procedure<br>• OOS and investigation<br>• Material release<br>• Self-inspection and vendor qualification<br>• Validation and qualification<br>• Equipment calibration<br>• Data integrity<br>• Sampling and testing of materials<br>• Batch processing records<br>• Materials management system<br>• Purified water system<br>• HVAC system Rifa production area<br><br>**Site visited:**<br>• Starting material warehouse (Rifampicin and General)<br>• Rifampicin production operations<br>• QC laboratories including chemical and microbiological<br>• Stability chambers area |
| Restrictions | The focus of the inspection included storage, production quality control areas where WHO prequalification products were manufactured |
| Out of scope | Products not submitted to WHO for Prequalification |
| WHO product numbers covered by the inspection | The following dosage forms were inspected: tablets, film-coated tablets and dispersible tablets |

| Abbreviations | | |
|---|---|---|
| | AHU | air handling unit |
| | ALCOA | attributable, legible, contemporaneous, original and accurate |

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| 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 |

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| 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** |
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**1. Pharmaceutical quality system**

A pharmaceutical quality system (PQS) was established, with Quality Manual, Policies and written procedures covering essential GMP principles for the site. A Macleods Corporate Quality Manual was available and was briefly reviewed during the inspection. It was suggested to include appropriate text in QM incorporating and defining Oxalis role and operations. PQS included both corporate and site specific procedures. Procedures that were reviewed and discussed during the inspection were generally presented promptly, however not all of these procedures were sufficiently detailed or satisfactorily implemented, and both procedure content and implementation had to be improved.

**Product quality review (PQR)**

A PQR procedure was in place describing the steps to verify consistency of existing processes, appropriateness of established specifications for starting materials, in process and finished products as well as monitoring trends. According to the procedure a monthly program was issued and PQR had to be completed within 30 days from the date specified in the plan. Where no batches were manufactured the previous year PQR was performed at the end of the year. Nevertheless it was noted that certain quality attributes were not appropriately trended and statistically analyzed.

**Quality Risk Management (QRM)**

A QRM procedure was available. FMEA was identified as the main tool for risk assessment. QRM was widely applied on all manufacturing operations including but not limited to change control and deviation management, production and complaints.

**Change and deviation management**

The company had procedures in place for change and deviation management. The procedure on handling of changes adequately described the stages of initiation, evaluation, approval, implementation and review. Two types of changes were defined: documentation and facility related. The proposed changes had to be justified by the head of the relevant department and a unique number was assigned by QA department. Changes were categorized as major, moderate or minor, based on nature and impact. QA head evaluated the need of carrying out a formal risk analysis and the proposed change had to be approved by Macleods Corporate QA. Changes in documentation had to be implemented within 3 months and facility related changes had to be completed within 6 months. Extensions were granted based on appropriate justification. A quarterly review of changes was conducted.

Deviations were categorized as planned and unplanned and based on their criticality they were categorized as minor, major and critical. Root cause investigations were conducted and relevant CAPA were identified and

implemented. Extensions were documented and could be granted upon justification. 2016 and 2017 deviation registers were presented and reviewed.

**CAPA management**

A CAPA management procedure was presented. It sufficiently described a system for conducting and documenting activities for remedial actions and continual assessment of compliance. CAPAs relating to 2016 and 2017 deviations reported above were checked.

**Investigation of Out Of Specification**

OOS investigations were performed according to a written procedure and investigations were carried out in two phases. In Phase 1 the assignable cause was identified and reanalysis of the sample was performed. If an assignable cause was not identified a cross functional investigation was initiated. If the cause could not be determined a Phase 2 investigation was initiated where resampling was allowed. There were different procedures for handling OOS for packaging materials and microbiological results. OOS investigations were checked during PQR review and during the laboratories visits

A procedure for handling Out Of Trend (OOT) results was also presented. The procedure was applicable to all OOT results obtained during analysis of stability samples, finished product samples and in process samples.

**2. Good manufacturing practices for pharmaceutical products**

Basic principles of good manufacturing practices were appropriately described, and implemented. Manufacturing processes were adequately defined and documented in BMRs and BPRs. Required resources were available, including adequate premises, equipment and utilities. Appropriately qualified personnel were employed. Similarly to the previous WHO inspection all areas visited were generally clean, tidy and well-maintained.

**3. Sanitation and hygiene**

Premises and equipment were generally maintained at an acceptable level of cleanliness and they were appropriately labelled. There was a pest control programme in place

**4. Qualification and validation**

The key principles of qualification and validation program were defined and documented in the Validation Master Plan.

**5. Complaints**

The company had in place a procedure on registering, investigating and monitoring complaints. They were classified as critical, major and minor and root cause investigations were carried out by QA. In case of critical complaints there was a provision to inform authorities within three working days. Impact was determined by applying the risk management SOP. Trend analysis was performed quarterly and annually to detect recurrence. Macleods CQA was informed within 24 hours from receipt of a complaint.

**6. Product recalls**

A product recall procedure was available. Head QA was responsible for triggering the recall procedure and Macleods Head CQA convened the recall committee which approved the recall proposal. Recalls were categorized in three classes and relevant authorities were notified. Information relevant to product/batch distribution were collected and wholesale distributors were informed accordingly, in a timely manner. The

final recall report was compiled 2-4 weeks from the initiation of the recall. A mock recall was performed annually. The 2017 mock recall was reviewed.

**7. Contract production, analysis and other activities**

The company was an exclusive contract manufacturer for Macleods. A technical agreement between the companies defining responsibilities of both parties was presented. The contract adequately addressed the observations of the previous WHO inspection. Installation and partial qualification of the extension of the PW distribution system was carried out by a third party. No technical agreement between the companies was presented.

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

Self-inspection was not reviewed in detail. A vendor qualification procedure was in place.

**9. Personnel**

Organization charts were available reflecting administrative structure. In general personnel met during the inspection appeared aware of the basic principles of GMP. Job descriptions of the production manager, QC and stores managers were checked as well as the job description of the microbiological laboratory executive.

**10. Training**

Training of personnel was performed according to an established procedure. New employees had to undergo induction training and general training followed by "on the job training", where they performed their duties under the supervision of more experienced personnel. Training records of new employees from production and quality control were reviewed. Continuous training for personnel was foreseen and performed according to an annual training program which was compiled at the beginning of each year based on proposals from departments' heads and approval by QA. Training programs for 2017 and 2018 and their implementation were reviewed. Evaluation of training was performed either orally or by written questionnaires. In case of failure, retraining was foreseen. A list of trainers was available. For contract workers there was a general training program focusing on their duties (housekeeping in secondary packaging area and in warehouses Relevant records were reviewed.

**11. Personal hygiene**

Personnel gowning procedure was appropriate and was generally followed. Instructions and pictorials to be followed were sufficiently clear when it came to personal hygiene. Spot checks on medical records of personnel were performed

**12. Premises**

Storage areas for warehousing of raw materials and finished product were of sufficient capacity. Temperature and humidity were monitored. Receiving and dispatch bays were separated and were protected from weather conditions. In 2016 an extension to G block was constructed introducing a new Rifampicin dedicated area. The new area included on the ground floor receiving area, quarantine area and 3 sampling booths. A new warehouse in the Rifampicin area was established. One sampling booth was dedicated to Rifampicin sampling. Excipients and APIs used in the General block were sampled and dispensed separately. There were two dispensing rooms in the Rifampicin area. One dispensing room was dedicated to Rifampicin. On the second floor secondary and tertiary packaging storage areas were established. MDI production was transferred on the first floor. There were separate change rooms for men and women. New AHUs were installed with pre-filtration and terminal HEPA filtration. The following parameters were

assessed during qualification: air velocity and air changes, filter integrity, differential pressure, airflow pattern, temperature and relative humidity, recovery time, non-viable and viable particles measurements, sound level, light intensity, air flow pattern. Preventive maintenance and cleaning of AHUs was performed according to an established procedure and relevant logbooks and records were reviewed. Monitoring of differential pressure across AHU filters was performed. Quality control laboratories were separated from production areas.

**13. Equipment**

In general equipment was appropriate for the manufacture of solid dosage forms. Records for calibration, qualification and maintenance were available. Due to a new extension built in General Block, PW distribution system was modified introducing new user points. Qualification of the system was reviewed as well as the 2017 monitoring report. A procedure for sampling, testing and releasing purified water was presented. Quality of water was tested chemically and microbiologically (PW from the return part of the distribution loop, was tested daily). Some discrepancies regarding passivation and sampling operations were identified.

**14. Materials**

There was a procedure in place describing receipt and storage of raw materials. A check list was used for receipt of raw materials. Material stock and status were managed via an ERP system. A unique material code was assigned to each material in the system. Procedures for material sampling and dispensing were available. Temperature and Relative Humidity were monitored and controlled.

**15. Documentation**

A documentation system was in place. Procedures defined and supported manufacturing and quality control operations. In general documents were approved, signed and dated by appropriate responsible persons, reviewed and kept up to date. Specifications and testing procedures were available. Some discrepancies in distribution of documents were identified

**16. Good practices in production**

A visit to production areas in G block was made. At the time of inspection there were ongoing production operations. Areas inspected included sampling booths, dispensing areas, granulation, compression rooms, coating rooms and primary and secondary packaging areas. Product dedicated, FBD filter bags were used and they were appropriately marked and stored. BMRs and BPRs of batches being manufactured during the tour were spot checked as well as maintenance and calibration of equipment.

**17. Good practices in quality control**

Quality control laboratories were separated from production areas. Chemical laboratories were visited as well as the separate areas where stability chambers were installed. The QC lab was well organized and equipped. Analytical equipment were installed in separate rooms and logbooks for use and maintenance of equipment were presented. Different roles and access rights (analyst, reviewer, service engineer, and administrator) were established for UV and IR equipment. However, audit trail functionalities were not installed. The company had identified this flaw and had already initiated a change control. Reference and impurities standards were kept and their consumption documented. Although, there was an SOP in place for establishing working standards, Macleods supplied Oxalis with all working standards. Stability samples were stored in 4 different chambers (30°C 65%RH, 40°C 75%RH, 25°C 60%RH, 30°C 75%RH) which were installed in a separate room. An inventory of stability samples for each chamber was maintained.

Practices in the Microbiological laboratory were also reviewed. Procedures and records for preparation of culture media, growth promotion and consumption of materials and reagents were spot checked.

**Part 3: Conclusion**

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as the Corrective Actions taken and planned, ***Oxalis Labs, Village Theda, P.O. Lodhimajra, Tehsil Baddi, Distt. Solan (H.P), India*** was considered to be operating at an acceptable level for compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full inspection report as well as those reflected in the WHO Public Inspection Report (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 used for assessing compliance***

1. 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

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.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
   ***Short name: WHO TRS No. 986, Annex 2***

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

4. 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/

5. WHO guidelines for sampling of pharmaceutical products and related materials. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report* Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   ***Short name:*** *WHO TRS No. 929, Annex 4*

http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

6. 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
   ***Short name: WHO TRS No. 961, Annex 5***
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

7. 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

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

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

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 prosecution of antimalarial active pharmaceutical ingredients. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
***Short name: WHO TRS No. 992, Annex 6***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
***Short name: WHO TRS No. 996, Annex 3***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

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

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