

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

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| Part 1 | General information |
| Manufacturers details | |
| Company information | |
| Name of manufacturer | Getz Pharma. Pvt Ltd |
| Corporate address of manufacturer | 29-30/27 Korangi Industrial Area, Karachi, 74900, Pakistan |
| Inspected site | |
| Address of inspected manufacturing site if different from that given above | 29-30/27 Korangi Industrial Area, Karachi, 74900, Pakistan |
| Unit / block / workshop number | OSD Block, Main production building |
| Manufacturing license number | No.000284 |
| Inspection details | |
| Dates of inspection | 21 - 24 August 2017 |
| Type of inspection | Re-inspection |
| Introduction | |
| Brief summary of the manufacturing activities | Production and quality control of FPPs including tablets, hard gelatin capsules, oral powders for suspension, parenteral (liquid & powder) and metered dose inhalers. |
| General information about the company and site | <p>Getz Pharma was established in 1995 at the current manufacturing site. Approximately 781 employees were employed at the site, of which 199 were technical staff. Another manufacturing facility where commercial production will commence from Q4 2018 was under construction (constructed area of 85,030 square meters)</p> <p>The site included production of OSD, liquid and sterile powder for injection, biotech products and metered dose inhalers (MDIs).</p> |

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| | The manufacturing of penicillin products had been discontinued since March 2016. The production and testing of Cephalosporin and Penicillin products were contracted out as stated by the company. |
| History | This was the 3 rd WHO inspection with the last being in September 2015. The first WHO inspection was for QC laboratory in 2103. The site has also been inspected by drug regulatory authorities of Ivory Coast, Tanzania, Ethiopia, Kenya, Yemen and Malaysia in the past three years. |
| Brief report of inspection activities undertaken | |
| Scope and limitations | |
| Areas inspected | <p>Document reviewed including but not limited</p> <ul style="list-style-type: none"> • Organization Chart • Job descriptions for key personnel • Product Quality Review • Quality Risk Management • Management Review • Responsibilities of the quality units and production • Complaints and Recalls • Deviation control and change control • OOS and investigation • CAPA procedure • Material release • Validation and qualification • Data integrity • Product release • Sampling and testing of materials • Batch processing records • Materials management system • Purified water system <p>Site visited:</p> <ul style="list-style-type: none"> • OSD Production operations with particular focus on Granulation suite 2, Compression Kosch XL-400, Coating XL-Cota. • Stability study QC laboratory and control system • Starting material and finished Goods warehouse |
| Restrictions | The tablet products manufactured on this site included the manufactured by dry, wet granulation and direct compressing process. A number of the company's products were also manufactured using processes other than the products under WHO pre-qualification for which the wet granulation was employed. Neither of other two processes was inspected during this inspection. |
| Out of scope | Products not submitted to WHO for Prequalification |

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| WHO product numbers covered by the inspection | Moxifloxacin Hydrochloride 400mg, Film-coated tablets (TB311) |
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| 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 | |

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| 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 |

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

1. Pharmaceutical quality system

General

A system for quality assurance was established, with procedures covering key quality elements in place. The procedures were reviewed and discussed during the inspection. Operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were appropriately specified in written job-descriptions. Product and processes were monitored and the results taken into account during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

Product quality review

Annual product quality review was performed according to a documented procedure. The WHO grade Moxifloxacin tablets has not been approved at the time of inspection. The product quality review for Moxifloxacin tablets 400mg for other specification/market was reviewed. The manufacturing process was same to the tablet applied for PQ but the product specifications were different. Change control and deviation for the relevant production equipment were selected and reviewed as examples.

Change and deviation management

The company had SOPs in place for change and deviation management. The procedures as described were generally of a good standard. Changes and deviations were managed in hard copy with reporting documents and the company was in the process to transfer all relevant information to the SAP system - but this had not been completed at the time of the inspection. Non-compliances observed during the inspection that was listed in the full report regarding deviation management was addressed by the manufacturer to a satisfactory level.

CAPA

The procedure was available for review. The log was manually handled.

Management review

Management review procedure was available for inspection. The review meeting was held once a year. The meeting minutes for 2016 were reviewed.

Quality Risk Management

The company's procedures on "Quality risk management" QRM were reviewed. This SOP discussed various risk assessment tools; Non-compliances observed during the inspection that was listed in the full report regarding quality risk management addressed by the manufacturer to a satisfactory level.

Data integrity management

As noted above policies and procedures have been introduced and updated to better assure data and record management systems. SAP system had been validated as corrective action to the observation made in last inspection. Adequate systems and documentation of this system were generally in place for the software and hardware system with much of the qualification being performed by the software vendor.

HPLCs, GC and IRs located in four QC labs were all standalone system. Data were backed up daily, weekly or monthly according to the data back up and restoration SOPs.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were implemented and followed. Required staff and system resources were provided. Manufacturing processes were clearly defined and documented. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and comprehensive records were made during manufacture.

3. Sanitation and hygiene

In general, premises and equipment were maintained at a satisfactory level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility, with appropriate hand washing facilities.

Clean areas were cleaned frequently in accordance with approved written procedures. Environmental monitoring of viable particles was regularly undertaken.

4. Qualification and validation

The company approach to validation was documented and explained in the Validation Mater Plan (VMP) and the VMP was briefly reviewed by the inspectors. The key elements of a qualification and validation programme were defined.

During the inspection computerized system validation procedures and validations for SAP system were briefly reviewed. They were considered generally acceptable.

Cleaning validation policy was presented for review. Products including Moxifloxacin tablet 400mg was in the residue calculation matrix; worst case approach was followed by the company.

5. Complaints

Complaints were handled according to a documented procedure and were classified as minor, major or critical, depending on the nature of the complaint. The 2016 complaint log book and records were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding complaints was addressed by the manufacturer to a satisfactory level.

6. Product recalls

The product recall was described as a policy rather than procedure. Non-compliances observed during the inspection that was listed in the full report regarding recall procedure was addressed by the manufacturer to a satisfactory level.

7. Contract production, analysis and other activities

According to the Site Master File, there was no use of external scientific, analytical or other technical assistance in relation to the products in the inspection scope. However, it could happen in future according to the additional tests required from the dossier review comments for the API testing in the scope.

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

Self-inspection was not covered in detail by this inspection.

A system of supplier approval was in place and managed in the SAP system. The material used for commercial batches was listed in the SAP and for R & D purpose was with manual system. Records for Moxifloxacin API suppliers were reviewed and were generally satisfactory.

9. Personnel

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsibilities of staff, and their specific duties were recorded in written job descriptions. Personnel interviewed during the inspection were aware of the principles of GMP in general. An organization charts and job descriptions were available and considered acceptable.

10. Training

Training was not covered in detail by this inspection.

11. Personal hygiene

Changing and washing before entry to production areas followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. No concerns of note were identified during the inspection. The approach to sanitation and hygiene was in general acceptable.

12. Premises

Generally premises were located, designed, constructed and maintained to suit the operations to be carried out. The layout and design of premises minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination. OSD and sterile injection products were manufactured in the same building and physically segregated.

Manufacturing areas were generally of a good standard and suitable for the activities conducted therein. Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning.

Storage areas were of sufficient capacity. Receiving and dispatch bays were separated and protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products.

QC laboratories were separated from production areas. Adequate space was provided for samples, reference standards, solvents, reagents and records.

13. Equipment

The equipment installed for tablet manufacturing was of a good standard. The facility and equipment appeared to be running well with no significant stoppages on either line noted during the inspection. The detailed procedures for the operation of key equipment were generally well documented.

Laboratory equipment and instruments were suited to the testing procedures undertaken in general, however, the company has not considered to network the analysis instruments including HPLC, GC and IR.

The design and qualification of water system was briefly reviewed. Non-compliances observed during the inspection that was listed in the full report regarding purified water system was addressed by the manufacturer to a satisfactory level.

14. Materials

Starting materials and packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure areas.

Finished products were held in quarantine in production area until their final release, after which they were transferred to and stored under appropriate and monitored conditions in a separate store, in a different building across the road.

Rejected materials and products were marked as such and stored in designated secure areas. Two WHO registration batches had already expired and these were moved into the rejected area in the finished goods warehouse, appropriately labelled.

15. Documentation

In general, documentation was designed, prepared, reviewed and distributed according to a documented procedure. Documents were regularly reviewed and kept up to date.

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products of Moxifloxacin.

Batch manufacturing records (BMRs) were retained for each batch processed. Before any processing began, checks were made that the equipment and work stations were clear of previous products, documents, or materials, and that the equipment was clean and suitable for use. Checks were recorded as part of the BMR. Batch records were with each process stage requiring multiple pages. Master formula was saved in the SAP system and records were paper based.

A batch packaging record (BPR) was retained for each batch packaged. Before any packaging operation began, checks were made that the equipment and work station were clear of previous products, documents or materials, and that equipment was clean and suitable for use. The sample of BMR and BPRs reviewed were generally satisfactory.

16. Good practices in production

A brief visit to production areas was undertaken. The premises were relatively new and in a good state. Areas briefly inspected included the dispensing areas, a granulation area where production of Moxifloxacin was done, compression area, and coating suite. The areas were generally clean and well maintained. According to the layout, areas were classified as Grade D. The production was in operation at the time of inspection.

Moxifloxacin tablet for WHO PQ was validated with specified Granulation Suites, Compression and Coating equipment.

17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that the QC arrangements are effectively and reliably carried out in general.

There were several QC laboratories including chemical, packaging and microbiology QC laboratories. The lab for stability studies was briefly inspected. The stability testing specifications, testing data, standardization of working references were reviewed.

OOS

SOP on OOS investigation and the OOS log book for 2016 and 2017 were reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding OOS management were addressed by the manufacturer to a satisfactory level.

Stability Testing

A written programme for stability study was available. Stability study program for Moxifloxacin tablets was reviewed. The stability testing for registration batches was performed by R & D department and the results in the HPLC were checked. The data management was discussed.

PART 3

Initial 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, Getz Pharma. Pvt Ltd. located at 29-30/27 Korangi Industrial Area, Karachi, 74900, Pakistan was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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 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.
Short name: WHO TRS No. 986, Annex 2
<http://www.who.int/medicines/publications/44threport/en/>

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
Short name: WHO TRS No. 957, Annex 2
<http://www.who.int/medicines/publications/44threport/en/>
3. WHO 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
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. 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](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
Short name: WHO TRS No. 937, Annex 4
[http://whqlibdoc.who.int/trs/WHO TRS 937_eng.pdf?ua=1](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 TRS No. 961, 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](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](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](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. Fifties 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. Fifties 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. Fifties 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
24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties 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