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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**MSN Laboratories Private Limited, Formulations Division, Unit-II,**
Corporate address of manufacturer	MSN House, Plot No.: C-24, Industrial Estate, Sanath Nagar, Hyderabad-500 018, Telangana, INDIA. Tel: +91-40-30438660 Fax: +91-40-30438798
Inspected site	
Address of inspected manufacturing site if different from that given above	MSN laboratories Private Limited, Formulations Division, Unit-II, Sy. No. 1277 & 1319 to 1324, Nandigama (Village & Mandal), Rangareddy District – 509 216. Telangana, INDIA. Tel: +91-40-30449200 Fax: +91-40-30449211
Unit / block / workshop number	Unit-II
Manufacturing license number, (delete if not applicable)	Manufacturing license has been issued by the State Drugs Control Administration (DCA), Hyderabad, Telangana, India. The site manufacturing license number is 5/MN/TS/2014/F/G and is valid up to 24/08/2019.
Inspection details	
Dates of inspection	20-23 March 2017
Type of inspection	Initial GMP inspection
Introduction	
Brief summary of the manufacturing activities	The manufacturing facility is situated at Nandigama, Telangana state. Geographically it is located at 17°05'43.3" N and 78°14'48.8" E. The factory is situated at Sy. No.: 1277 & 1319 to 1324, Nandigama Village & Mandal, Rangareddy, District – 509 216, Telangana, and about 45 kilometers from Hyderabad. The site is about 20 km (on national highway to Bengaluru) far from Rajiv Gandhi International Airport,

<table>
<tr><td></td><td>Shamshabad, Hyderabad, India.

<table>
<tr><td rowspan="4">Block D
(Total built-up area:15550 m^2)</td><td>Ground floor - Warehouse, Change rooms, administration.</td><td>~ 4300 m^2</td></tr>
<tr><td>Mezzanine floor - QA, Conference hall, training hall, visitors dining, technical area.</td><td>~ 2645 m^2</td></tr>
<tr><td>First floor - QC and production area.</td><td>~ 4300 m^2</td></tr>
<tr><td>Second floor - Purified water system, stability chambers room, control samples room, AHUs technical area, offices.</td><td>~ 4300 m^2</td></tr>
</table>
The site is also authorized to manufacture tablets and capsules of General therapeutic category in Block-D, which is dedicated for Oral Solid Dosage (OSD) drug products.</td></tr>
<tr><td>General information about the company and site</td><td>MSN Laboratories Private Limited, Formulations Division, Unit-II, Nandigama is a unit of MSN Laboratories Private Limited and it belongs to MSN Group of companies established in the year 2003. MSN Group comprises a number of API manufacturing plants, two finished dosage facilities and a separate dedicated Research & Development center.

Currently, the site contains five major independent buildings. Two of them are manufacturing blocks (Block C and Block D). Details of the five blocks are as follows;
a) Block A: Security building
b) Block B: Boiler House
c) Block C: Manufactures Oncology Drug Products
d) Block D: Manufactures General Drug Products
e) Block E: Utility block</td></tr>
<tr><td>History</td><td>This was the first WHO-PQT inspection of this site.
The facility of General OSD i.e. Block-D has been audited by USFDA in the February 2015 & February 2016 and by Indian Drug Authorities in April2015 and in October 2015.</td></tr>
<tr><td>Brief report of inspection activities undertaken</td><td></td></tr>
<tr><td>Scope and limitations</td><td></td></tr>
<tr><td>Areas inspected</td><td>Pharmaceutical quality system
Personnel
Qualification and validation
Quality control
Production</td></tr>
<tr><td>Restrictions</td><td>None</td></tr>
<tr><td>Out of scope</td><td>Block C (oncology)
Area currently under expansion in Block D</td></tr>
<tr><td>WHO product numbers covered by the inspection</td><td>Levofloxacin Tablet, Film-coated 250mg (TB338)
Levofloxacin Tablet, Film-coated 500mg (TB339)
Levofloxacin Tablet, Film-coated 750mg (TB340)</td></tr>
</table>

	Moxifloxacin Tablet, Film-coated 400mg (TB341)

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance

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

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

Brief summary of the findings and comments

1. Pharmaceutical quality system

The quality management system procedures and instructions in the site were developed based on the requirements sited in international GMP guidelines and regulations like 21 CFR part 210 and 211, US FDA Guidance's for industry, EU GMP guidelines for Medicinal products, PIC/s GMP guidelines for Medicinal products, WHO GMP main principles for pharmaceutical products, ISO Standard 9001-2008, ICH Q9, ICH Q10, etc. and also based on Indian GMP regulations i.e. Schedule-M.

Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and results considered in batch release decision; regular reviews of the quality of pharmaceutical products were conducted.

The procedures related to product quality review, quality risk management, deviations, change controls and corrective actions and preventive actions were reviewed.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Good manufacturing practices for pharmaceutical products

Manufacturing processes were defined and reviewed by the inspection team. Qualifications and validations were performed. Significant deviations were recorded and investigated, root causes were determined and CAPAs were implemented. Systems were in place for handling complaints and recalling any batch of product from sale or supply.

The Block D was a multi-purpose shared facility which produced non-sterile oral solid dosage forms. Most of the equipment inspected were operated in closed conditions thereby reducing the risk of contamination and cross contamination.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Sanitation and hygiene

The company had an SOP as the basis for its approach to personal hygiene and sanitation in its production facilities. Microbial monitoring of the production area was performed once a month.

4. Qualification and validation

Validation master plan/VMP was discussed. The VMP covered objective, scope, organizational structure, equipment qualification policy, facility qualification, utility, water system, process validation, hold time study, computerized system qualifications, analytical method validation, product transportation study etc. It was noted that equipment were re-qualified once/5 years or whenever a change was made. Software' was be re-qualified if there was a change in software version.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

5. Complaints

The SOP for handling market was available. The QA had the responsibility for handling and organizing the investigation of complaints, which were categorized as critical, major, and minor. The period for completing a complaint investigation was 30 days. None of the products had been commercialized at the time of inspection. Therefore, no complaints were received.

6. Product recalls

The SOP "Product recall and Rapid Alert System" was available. The SOP was based on CDSCO/RRS (the central drugs, India), Rev:00 2012, PIC/S, WHO TRS, 961, Annex 3, EP Chapter 8, Complaints, Quality defects and Product recalls. Recalls were divided into three classes: Class I – High probability that this situation would cause serious adverse health or death, Class II – Temporary adverse health and Class III – Not likely to cause any adverse health consequences.

A mock recall using tablets was initiated and completed to assess the recovery. The product was distributed widely in India. From all places, 100% recovery was achieved. The company intended to carry out another mock recall once the extent of international markets became apparent after the product approval.

7. Contract production, analysis and other activities

Contract production activity was not inspected due to time constraints. For contract testing activities, refer chapter on "Good Practices in Quality Control".

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

The SOP was discussed. A list of internal auditors was also available. Training of auditors was conducted by outside consultants and certificates were available. Self-inspections were scheduled twice a year. All departments were covered. Deficiencies were classified as critical, major and minor. The last inspection was conducted in March 2017. The report was not finalized at the time of inspection but some data were provided to assess the trend especially the effectiveness of CAPA for deficiencies found in "Procedures" previously. Deficiencies were trended. The outcome of the March 2017 inspection demonstrated that CAPA was effective in reducing various deficiencies.

9. Personnel

There were an adequate number of personnel qualified to perform and supervise the manufacturing and quality control. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

10. Training

An SOP was in place. Staff training included the following:

- New recruits (Induction and orientation)
- On job training
- cGMP training
- Safety training
- Specific training
- External training

The training schedule was purportedly discussed and prepared in a meeting of Head of Departments (HODs).

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Personal hygiene

All personnel, prior to and during employment, had to undergo health examinations. Regular health examinations were carried out every year. Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines was prohibited in production, laboratory and storage areas.

12. Premises

Rest and refreshment rooms were separate from manufacturing and control areas.

Storage areas were of sufficient capacity.

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Premises were cleaned and disinfected according to written procedures.

Sufficient space was given to avoid mix ups and cross-contamination. Storage space was provided for samples, reference standards, solvents, reagents and records.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Equipment

Fixed pipework was labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis.

Procedure for preventive maintenance was discussed which provided procedure for the preventive maintenance (PM) of production and utility equipment and instruments. It was indicated that PM was based on the criticality and recommendation from the vendors.

Procedure for qualification, requalification and periodic requalification of HVAC system, RLAFs, LAFs, Dynamic Pass box, and air showers was discussed. Periodic requalification report for Granulation 4 (area was discussed. Operation and preventive maintenance procedure of AHUs and dehumidifier / ventilation and exhaust units was discussed.

The water system was equipped with generation and distribution system wherein source water was checked for hardness (NMT 5ppm), passed through ultrafiltration (Conductivity NMT 100S/m) system before passed through reversed osmosis (RO) RO1, RO2 (conductivity NMT 20) and electro-deionization (EDI) (conductivity NMT 1.25S/m). The conductivity was monitored online. The return line was also connected with online conductivity meter (conductivity less than 1.25S/m), return flow (greater than 4200 l/h) and TOC (234ppb limit for alert and 500ppb limit for action). A total of 15 sampling points was identified, 14 user points and 4 from the generation system (EDI generation out, storage tank outlet, after UV and return line). Daily sampling was done for return line whereas the rest of user points were covered once per week. The sanitization was done on weekly basis using hot water (temperature over 80°C for 45 minutes) using a recipe verified on supervisory control and data acquisition (SCADA).

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Materials

Materials were received, sampled and tested according to the written procedures. Acceptable quality level (AQL) was applied for ampoules sampling.

Separate change rooms for staff and visitors equipped with toilets were available. Male change room was equipped with foot and hand wash machine and lockers were provided. At the time of inspection, there was no

activity performed in sampling and dispensing areas. The warehouse was found clean and well maintained. Mobile racking system was provided for the storage of quarantined and approved incoming starting materials. It was claimed that temperature mapping of raw material stores (1 & 2) and finished goods store was conducted for three seasons in loaded conditions. The hot spot was identified and temperature and humidity were monitored using min/max thermohygrometer. Separate material airlock (MAL) and personnel airlock (PAL) provided for sampling and dispensing cubicles. Separate sampling and dispensing rooms were identified for the sampling and dispensing of actives and excipients respectively. It was noted that dry cleaning was used for the cleaning of sampling area for the same material whereas wet cleaning was used for different APIs.

Supplier qualification and approval procedure was discussed. Before procuring materials, MSN sent questionnaire to seek information about the GMP standard and list of products etc.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Documentation

Documents were available and included SOPs, protocols and records. SOPs were generally followed. Issuing of documents, formats were not always appropriate.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

16. Good practices in production

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Access to production premises was restricted to authorized personnel. The General Oral Solids Dosages (OSD) also known as Block D was a multi-purpose shared facility, which produced non-sterile oral solid dosage forms. Block D was designed to manufacture a wide range of oral OSDs, Tablets, Capsules of General therapeutic categories.

All the critical areas in General Oral Solids Block (Block D) were classified as per EU GMP grade D at rest occupancy state (approximately equivalent to ISO 14644-1 Class 8 at rest occupancy state). The process corridors were positively pressurized as compared to atmosphere and the pressure was maintained about 4.0 mm of water column. Separate personnel and material entries were provided for all process areas and maintained 3.0 mm of water column. The process areas were kept at a negative pressure as compared to the process corridors, which were maintained at a pressure of 2.0 mm of water column. The return air was passed through return air filters (20µ) and 90% of it was again re-circulated with intake of about 10% fresh air through 10µ filter. Filters in an AHU were arranged in the series of 10µ, 3µ, 0.3µ (terminal HEPA) filters respectively.

At the time of inspection, some activities were underway in the granulation area 4.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

17. Good practices in quality control

The QC function was independent from other departments. Adequate resources and equipment were available to ensure that all the QC-activities were carried out. QC personnel had access to production areas for sampling and investigations as appropriate.

Microbiology laboratory was common for both Blocks (General Oral Solids Dosages Block D and Oncology Block C). It was not inspected due to time constraints. Control sample room was equipped with compactors for sample storage, and it was monitored for temperature and humidity twice a day. The area was found to be clean and tidy.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

PART 3
Conclusion

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, MSN Laboratories Private Limited, Formulations Division, Unit-II, Sy. No. 1277 & 1319 to 1324, Nandigama (Village & Mandal), Rangareddy District – 509 216, Telangana, India, located at 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

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

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

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

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

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

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

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

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

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

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

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

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

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

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

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

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 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 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 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 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 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 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf