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**Prequalification Team**
**WHO PUBLIC INSPECTION REPORT**
**(WHOPIR)**
**Active Pharmaceutical Ingredient Manufacturer**

| **Part 1** | **General information** |
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| **Manufacturer Details** | |
| Company information | |
| Name of manufacturer | Zhejiang Huahai Pharmaceutical Co Ltd |
| Corporate address of manufacturer | Zhejiang Huahai Pharmaceutical Co., Ltd<br>Xunqiao, Linhai, Zhejiang Province 317024, China |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | Costal Industrial Zone, Duqiao, Linhai, Zhejiang, 317016, China<br><br>DUNS number: 421262001 |
| Unit / block / workshop number | Nevirapine - Workshop 5 |
| CRM Inspection Record Number | INSP-2015-003 |
| **Inspection details** | |
| Dates of inspection | 26 – 29 June 2017 |
| Type of inspection | Routine GMP inspection |
| **Introduction** | |
| Brief summary of the manufacturing activities | Zhejiang Huahai Pharmaceutical Co. Ltd manufactures a range of intermediates and APIs at the site. No hormones, steroids, cephalosporins, beta-lactams or cytotoxics are produced at this site. |
| General information about the company and site | Zhejiang Huahai Pharmaceutical Co. Ltd. was established in January 1989 with corporate headquarters at Xunqiao, Linhai, Zhejiang Province, 317024, China. The company listed on the Shanghai Stock Exchange in March 2003.<br>The site inspected was located in a national medicine & chemical zone, Duqiao, Zhejiang Province and started operations in 2005.<br>The site was divided into East and West Zones. In total there were over 30 workshops at the site, with each workshop having its own API finishing area. There were 2 QC laboratories at the site; one at each zone. The production blocks where Nevirapine and Efavirenz |

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| | APIs (pilot batches) were manufactured, were located in the East Zone. |
| History | The site was regularly inspected and licensed by the Chinese Food and Drugs Administration. This was the third inspection conducted by WHO PQP; the first being in September 2011 and the last in April 2014. The scope of previous WHO inspections was Nevirapine (APIMF76) only.<br>The company stated the site had also been inspected for Nevirapine API manufacture and approved by BGV (2011), ANVISA, Brazil (2012), USFDA (2014) and May 2017(pending)) and COFEPRIS, Mexico (2014). |

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| **Brief report of inspection activities undertaken** | |
| **Scope and limitations** | |
| Areas inspected | The inspection focused on the production and control of Nevirapine and Efavirenz APIs.<br>For Nevirapine API, the inspection covered all the sections of WHO good manufacturing practices for active pharmaceutical ingredients including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.<br>For Efavirenz, see restrictions below. |
| Restrictions | Although Efavirenz API was included in the original scope of the inspection, at the time of the onsite inspection the company had only manufactured 3 pilot batches in a multi-product pilot facility. In addition, a new dedicated workshop for Efavirenz API was under construction with completion and transfer of product due before end 2017.<br>During the early stages of the inspection it became evident that it would not be possible to establish GMP compliance for this API under the circumstances. The matter was discussed with the company and as a result, the company provided a written request to exclude Efavirenz API from the scope of the inspection. |
| Out of scope | All aspects not relevant to the manufacture of Nevirapine API. |
| WHO product numbers covered by the inspection | APIMF76 – Nevirapine API |
| Abbreviations | SOP – standard operating procedure<br>API – active pharmaceutical ingredient<br>FPP – finished pharmaceutical product<br>PQS – pharmaceutical quality system<br>PQR – product quality review<br>QRM – quality risk management<br>CAPA – corrective actions and preventive actions<br>PpK – Process performance indice<br>CpK – Process capability indice<br>MR – management review<br>BMR – batch manufacturing record<br>BPR – batch packaging record<br>MF – master formulae<br>LAF – laminar air flow<br>AHU – air handling unit<br>FBD – fluid bed dryer<br>HVAC – heating, ventilation and air conditioning |

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| | CC – change control<br>RA – risk assessment<br>CoA – certificate of analysis<br>HPLC – high-performance liquid chromatograph<br>GC - gas chromatograph<br>UV - ultraviolet-visible spectrophotometer<br>IR – infrared spectrophotometer<br>FTIR - Fourier transform infrared spectrometer<br>TLC – thin layer chromatography<br>LOD – loss on drying<br>KF – Karl Fisher<br>NMR - nuclear magnetic resonance spectroscopy<br>NRA – national regulatory agency<br>URS – user requirements specifications<br>DQ – design qualification<br>IQ – installation qualification<br>PQ – performance qualification<br>OQ – operational qualification<br>FAT – factory acceptance test<br>MB – microbiology<br>TAMC – total aerobic microbial count<br>FMEA - failure modes and effects analysis<br>FTA – fault tree analysis<br>PHA - process Hazard Analysis<br>HACCP - hazard analysis and critical control points<br>PM - Preventive maintenance<br>WHOPIR – WHO public inspection report<br>EM – environmental monitoring<br>LoD – Limit of detection<br>BDL – Below detection limit |

| **Part 2** | **Brief summary of the findings and comments (where applicable)** |
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## 1. Quality management

The Quality Unit included a QA function and QC function, each reporting separately to the General Manager. Responsibilities of the Quality Unit and Production unit were clearly described through an organization chart, position descriptions and in relevant SOPs.

The organization chart and job descriptions for the QA Director and QC Director were reviewed and were acceptable.

The self-inspection program was not reviewed during this inspection.

PQRs were conducted on an annual basis according to an annual product review management system. The required elements had been considered and documented, and were mostly found acceptable. Non-compliances observed during the inspection that were listed in the full report regarding PQR were addressed by the manufacturer to a satisfactory level.

The 2016 PQR for Nevirapine was reviewed and generally found acceptable. The review included all the required elements and concluded that the manufacture of Nevirapine API was well controlled.

Quality risk management (QSM) was required to be performed according to a standard management procedure (SMP). The principles of QRM applied at the site and responsibilities for this activity were well documented. Two examples of the application of QRM at the site were reviewed: risk analysis for solvent recovery and risk assessment for facilities cross-contamination. Both were considered generally acceptable.

Finished API release was conducted according to an SOP. Responsibilities for the various stages of API release were satisfactorily described and relevant release forms were attached to the SOP. The release records reviewed were satisfactory.

## 2. Personnel

There appeared to be sufficient personnel for the activities undertaken and key personnel were suitably qualified with appropriate tertiary qualifications and experience in the manufacture of API products.

GMP training requirements were described in a SMP. The HR Department was responsible for managing the overall training system. Three levels of training were described; company level, department level and on the job training. For major topics in a training session, assessment was conducted by a written test with a specified pass mark.

Health requirements for personnel were described and direct contact with intermediates or APIs was avoided. Protective clothing and hygiene requirements such as hand washing, was appropriate to the nature of the particular manufacturing area.

## 3. Buildings and facilities

Buildings and facilities used in the manufacture of Nevirapine intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations appropriate to the type and stage of manufacture. The final purification, drying and packaging for the inspected API was performed in grade D areas.

Workshop 5 was dedicated to the manufacturer of Nevirapine and Hydrochlorothiazide with the Final stages conducted in a grade D area. Workshop 5 was generally considered suitable for the activities carried out.

Nitrogen gas supply was installed in a defined building with steam supplied from a central steam generation plant. Auxiliary power generation equipment was located in a separate dedicated building. Each workshop was equipped with its own compressed air supply. These utilities were not inspected.

Purified water was used in the final purification of Nevirapine and certain equipment cleaning. Potable water was used for intermediate steps. The purified water system was not inspected during the inspection. However, the overview of the results of regular quality monitoring indicated that the system was under satisfactory control.

## 4. Process equipment

Equipment used for the manufacture of Nevirapine intermediates and finished API were generally of a good standard and considered suitable for intended use. Where possible the equipment used to produce Nevirapine was dedicated to minimizing the possibility of cross-contamination. Other equipment, including for final purification, were shared with Hydrochlorothiazide. Centrifuge bags were dedicated to for Nevirapine.

Equipment was cleaned according to documented SOPs and records maintained. Status labels indicated the status of each equipment. All those reviewed were satisfactory.

Where necessary, measuring equipment was labelled with a calibration tag. All reviewed were within the calibration date.

Preventative maintenance requirements for each equipment were described in documented SOPs. A manual preventive maintenance plan was available. As an example, an SOP for the maintenance of centrifuges was reviewed. The SOP included a list of actions to be performed regularly. The record reviewed was satisfactory.

### 5. Documentation and records

The overall document control system was described in an SOP. This SOP included the various types of documents, including BMRs, their numbering, approval and control.

Various SOPs and records such as equipment cleaning and maintenance records, records of raw materials, packaging materials, production batch records and laboratory control records were reviewed during the inspection and generally found satisfactory. The SOP for the batch numbering system management was reviewed and discussed.

Three complete batch manufacturing records for Nevirapine were selected for review from PQR records and warehouse stock. All were generally considered satisfactory.

## 6. Materials management

Material suppliers were required to be approved, but the system for this was not reviewed during this inspection. A list of approved suppliers was available in a warehouse.

Starting materials were received according to a documented procedure. The procedure included cleaning of containers, a check for damage and a check for approved supplier. They were then placed in quarantine which was designated by label and tape.

Sampling of starting materials was performed by QC personnel according to an SOP. Appropriate environmentally controlled sampling areas were available in the warehouse. An SOP for the operation of the vertical flow sampling bench was reviewed. Each container sampled was marked with a "sampled" sticker and after testing and release by QC, was labelled with a "release" label.

An SOP for material code management system for materials and products was reviewed. The material code list presented for inspection was product specific.

Finished APIs were stored in a temperature and humidity controlled warehouse. All controls were generally found satisfactory.

## 7. Production and in-process controls

Production operations in workshop 5 were inspected and generally found acceptable. There was a system to indicate the status of the equipment. Reactors were appropriately labelled with the batch in process and the associated batch documentation was up to date. They were regularly cleaned and maintained according to approved procedures and records were maintained.

There were in-process controls conducted at appropriate stages of synthesis to monitor the quality of the intermediates and APIs. IPC testing to monitor quality was carried out by QC and there were written test procedures that described the tests to be performed.

## 8. Packaging and identification labelling of APIs and intermediates

Packaging materials were purchased from approved suppliers, placed in quarantine on receipt, sampled and tested by QC before release and stored in a suitably controlled warehouse.

Blank API labels were externally printed and sampled/tested by QC before release. Depending on the order, finished API labels with product specific information were printed as required. Checks on the correctness of printed finished API labels were performed and recorded.

Labels used on containers included at least the API name and identifying code, the batch number of the product, the retest date, the storage conditions and the name and address of the manufacturer.

Packaging and labelling was performed in areas dedicated for this purpose.

## 9. Storage and distribution

Starting materials, packing materials and finished API were stored in suitable warehouses. Some bulk solvents were stored in a tank farm. Controls were generally considered satisfactory.

Finished APIs were stored in a temperature and humidity controlled area. Records reviewed indicated that control was satisfactory.

## 10. Laboratory controls

The QC laboratories were responsible for physical, chemical and microbiological testing of starting materials, packaging materials, products (API's), environmental monitoring samples and purified water samples.

There were two separate QC labs located in the East and West zones. HPLC and GC were linked to the network with no standalone systems. There were dedicated rooms for activities related to sample receipt and storage, wet chemistry, instrumentation, and balance room. The laboratories were clean and well maintained. There were adequate number of equipment with up to date calibration status.

QC testing was conducted as specified in the relevant specification and according to documented testing procedure. WHO grade Nevirapine was tested with USDMF specification and consistent with the version in the dossier assessment report. Nevirapine Polymorph was tested by the corporate QC lab.

The OOS/OOT handling procedure was available and considered to be acceptable.

Microbiological quality control laboratory was located in the East zone. Media preparation and release, purified water testing and results monitoring were reviewed.

## 11. Validation

The company had policies, procedures, protocols and reports for validation and qualification of processes, procedures, equipment, utilities etc. An SOP for process validation was reviewed and appeared to be satisfactory.

Process validation for WHO grade Nevirapine with a specified code was performed in 2014 on four batches. The PV protocol and PV report were reviewed and generally appeared to be acceptable. The validation batches were tested with specification USDMF. The specification version had been updated at the time of this inspection.

## 12. Change control

Change control was managed according to written procedure. The change control register for 2015 and 2016 were checked. Non-compliances observed during the inspection that was listed in the full report regarding change control were addressed by the manufacturer to a satisfactory level.

## 13. Rejection and re-use of materials

Reworking and reprocessing requirements were described in an SMP "Reprocessing and Reworking Management Procedure". This procedure applied to APIs and intermediates and these activities were properly defined. Regulatory impact was considered during approval for rework, but it was understood that in practice batches are never reworked. If reprocessing was required, the reprocessed batch number would have an "R" suffix. Based on QA evaluation, a reprocessed batch may be added to the stability programme. There had been no rework or reprocessing for Nevirapine API during 2016 or 2017 to date.

Recovery of solvents and materials at different stages of synthesis was done according to documented instructions and were tested to meet predefined specifications. Solvent recovery was done on site. The in-house recovery processes were validated as part of the process validation. An SOP for the recovery of a solvent was reviewed and found satisfactory.

## 14. Complaints and recalls

Complaints were handled according to an SOP. They were required to be classified according to risk as "serious" or "other". Definitions of the terminology used were included in the SOP. According to the SOP, QA was required to evaluate complaints within 1 working day. The SOP specified that CAPA be undertaken if necessary and included a cross-reference to the CAPA SOP.

According to the available logs books and PQR, there had been no complaints regarding Nevirapine API during 2016 and 2017 to date.

The procedure for conducting recalls was not inspected. According to PQR records, there had been no recalls during 2016.

**15. Contract manufacturers (including laboratories)**

No contract laboratories or manufacturers were used for Nevirapine API.

**PART 3**

***Conclusion***

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, Nevirapine API (APIMF76) manufactured at Zhejiang Huahai Pharmaceutical Co Ltd, located at Costal Industrial Zone, Duqiao, Linhai, Zhejiang, 317016, China was considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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-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 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. 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

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 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

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

24. 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