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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	**THE GOVERNMENT PHARMACEUTICAL ORGANIZATION (GPO)**
Corporate address of manufacturer	Main Office, Main Facility and R&D 75/1 Rama VI Road, Ratchathewi, Bangkok Thailand.
Inspected site	
Address of inspected manufacturing site if different from that given above	Rangsit Pharmaceutical Production Plant 1, 138 Moo 4 Rangsit Nakhonnayok Road, Bueng Sanan, Thanyaburi, Pathumthani, Thailand, 12110
Unit / block / workshop number	Production Section 1 (Module 1: tablet manufacturing)
Manufacturing license number, (delete if not applicable)	Drug manufacturing license No.1/2552
Inspection details	
Dates of inspection	30 May - 2 June 2017
Type of inspection	Initial GMP inspection
Introduction	
Brief summary of the manufacturing activities	The Government Pharmaceutical Organization (GPO), Rangsit site is situated at 138 Moo 4, Rangsit, Nakhonnayok Road, Thanyaburi District, Pathumthani 12110 Thailand, 70 km from Bangkok city. The site which is located along Rangsit – Nakhonnayok Road is built on 158,400 sq. mts land. It borders Maha Vajiralongkorn Cancer Hospital towards North and a residential area towards West. Within the site, there are two separate facilities; Chemicals Department and Rangsit Pharmaceutical Production Plant 1 (RPP) each with separate warehouses for raw materials, packaging materials and finished goods, production sections for manufacturing and packaging as well as utilities. The pharmaceutical plant manufactures the general category of Oral Solid Dosage Formulation (Tablets and Hard

	Gelatin Capsules) since 2015, while the Chemicals Department manufactures active pharmaceutical ingredient (API); deferiprone since 1999 and Liquid for External use; rubbing alcohol since 2016.
General information about the company and site	The Government Pharmaceutical Organization (GPO) is a state enterprise under the Ministry of Public Health of Thailand. The main responsibility of GPO is to produce medicines and pharmaceutical products to support the country's public health section.
History	GMP Certificate (Tablets): Issued by Thai FDA in September 2016. This was the first WHO Prequalification inspection of RPP Thanyaburi, Pathumthani.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	See part 2
Restrictions	N/A
Out of scope	N/A
WHO product numbers covered by the inspection	Efavirenz Tablet, Film-coated 600mg (HA681)

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

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 the results were taken into account in batch release. Regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

It was noted that the computer systems the manufacturing site uses were:

- Werum software: manufacturing execution system: batch records, etc.
- Master control : eQMS, electronic quality management system including documentation management system
- Labvantage : LIMS system, quality control and lab testing is covered

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. Qualifications and validations were discussed to be performed according to prepared protocols. Significant deviations from the initial protocol were recorded and investigated, root causes were determined and corrective and preventive action were implemented. A system was available to recall any batch of product from sale or supply and complaints about marketed products were examined.

At the time of the inspection, the operation of coating and primary packing activity of Efavirenz 600mg film-coated tablets was going on, whereas the areas for primary packing activities were also running for other products as well.

The production was performed in a multi-product facility, as per company policy of one product at one time in Production Section 1 (Module 1: tablet manufacturing) and production equipment was not dedicated.

Adequate premises and equipment were available for production, in-process quality control and storage.

The manufacturing facility was located on a four- story building which consisted of four production lines. It was noted that Efavirenz 600mg film-coated tablets was produced in Production Section 1 (Module 1: tablet manufacturing).

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 clean room was performed as part of routine batch control.

Facilities were noted to be clean and well organized during the inspection.

4. Qualification and validation

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan (VMP). The VMP covered building and facilities, utility systems, equipment and processes, quality control laboratory validation, process, cleaning, analytical method validation, computerized system validation, calibration program and preventive maintenance.

Cleaning validation was performed and was capable of consistently removing chemical residues, cleaning agent's residues and microbiological contamination levels below acceptance limit from respective equipment.

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

5. Complaints

Handling of product complaint conducted according to SOP "Handling of Customer Complaints".

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

6. Product recalls

Product recall conducted according to SOP "Product recall and withdrawal". Recall effectiveness was stated to be evaluated by mock recall. There was no history of recalls for 2015 – 2017.

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

7. Contract production, analysis and other activities

Not inspected due to time constraints.

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

Self-inspection procedure was discussed. The procedure stipulated that self-inspection be carried out at least once every year. A list of auditors for six audit areas (warehouse, validation, compliance & QS, QC, production and engineering) was identified. A self-inspection schedule for 2017 was available.

Supplier qualification procedure was discussed. A flow chart was part of the procedure describing how new supplier is qualified.

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

9. Personnel

There appeared to be an adequate number of personnel qualified to perform and supervise the manufacturing and quality control. Controls were in place to prevent unauthorized people from entering production, storage and QC areas.

The number of personnel engaged in the Quality Assurance, Production, Quality Control, Warehouse, Engineer and other departments of Rangsit Pharmaceutical Production Plant 1 were as follows:

Division	Number of personnel
Administration	26
Production	215
Warehouse	55
Engineering	32
Quality Assurance	49
Quality Control	52
Total	429

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

10. Training

To support the knowledge of personnel, the company provides trainings. The training programs were arranged into a scheduled program. Training conducted according to the procedure of training for employee. Assessing the participants by questionnaire and the qualification score 80% was qualified, and < 80% not qualified.

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 an initial health examination. Thereafter regular health examinations were carried out every year. Direct contact between the operator's hands and starting materials, primary packaging materials and intermediate or bulk products was avoided. Smoking, eating, drinking, chewing, and keeping plants, food, drink; smoking material and personal medicines was prohibited in production, laboratory and storage areas.

12. Premises

The premises for manufacturing, storage and quality control of products were generally of a satisfactory standard. The production facilities of oral solid dosage (OSD) forms were together with tablets and hard gelatin capsules facilities situated in one building.

The inspected Production Section 1 (Module 1: tablet manufacturing) is a multipurpose area. The equipment and the facilities inspected were generally in good condition. Layouts of the facilities were available and up-to-date.

Premises were designed to have a logical flow of materials and personnel. The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. The company indicated that there are no other highly active products or non-pharmaceutical products manufactured in the area.

Warehouses were situated in the same building which separate from production area and materials and products were controlled by a computerized system.

Air handling system for Production Section 1 (Module 1: tablet manufacturing) was inspected.

QC laboratories including the microbiology laboratory were separated from production areas. Sufficient space was given to avoid mix ups and cross-contamination. Adequate 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

Equipment was located, designed and maintained to suit the operations to be carried out. Design of equipment permitted adequate cleaning and maintenance to avoid contamination and cross-contamination.

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.

Process equipment was installed and maintained in a way to minimize the risk of contamination and cross contamination. Production equipment was identified as to its content or purpose and cleanliness status.

The majority of the equipment is of European and Asian origin. The maintenance and cleaning status appeared good.

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 written procedures. Materials were stored under appropriate conditions established by the manufacturer in an orderly fashion. Starting materials and packaging materials were purchased from approved manufacturers and suppliers.

A brief inspection of the (electronically controlled material) warehouse was undertaken. Materials and finished products were stored in this store. The storage conditions (temperature and humidity) of the inspected products were controlled below 25^0C.

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

15. Documentation

Electronic and paper systems were in place for documentation management. Documents should be designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents had unambiguous contents: the title, nature and purpose were clearly stated. Documents were regularly reviewed and kept up to date.

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. Handling of materials and products was done in accordance with written procedures and, recorded.

Deviations were recorded and investigated in accordance with approved procedure. Operations on different products were not carried out simultaneously or in the same room. During processing, materials, bulk containers, major items of equipment, and the rooms and packaging lines being used, were labelled with an indication of the product or material being processed.

The inspected finished dosage form facilities were multi-product facilities. The Production Section 1 (Module 1: tablet manufacturing) has one tableting suite. It was noted that a total of 3 tablet products were produced in the Production Section 1 (Module 1: tablet manufacturing).

The temperature, relative humidity and air pressure differentials were monitored according to written procedures.

The site inspection of the production areas covered the following areas:

Production Section 1 (Module 1: tablet manufacturing):
- Granulation
- Blending
- Compression
- Coating
- Packing lines

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 were available to ensure that all QC arrangements were carried out in a timely and orderly fashion. QC personnel had access to production areas for sampling and investigations as appropriate.

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

The laboratory was inspected for residual impurities, optical rotation and particle size distribution. The inspection included the review of the logbook.

The SOP “Handling of out of specification (OOS)”, its flow chart and trends were discussed. A number of OOS investigation reports were discussed

The SOP “Handling of out of trend (OOT)” and its flow chart were discussed.

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, *The Government Pharmaceutical Organization (GPO), Rangsit Pharmaceutical Production Plant 1, located at 138 Moo 4 Rangsit Nakhonnayok Road, Bueng Sanan, Thanyaburi, Pathumthani, Thailand, 12110* 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