

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

Part 1	General information
Manufacturers details	
Company information	
Name of manufacturer	GPO-MBP Co., Ltd. Thailand.
Contact person	Mr Anan Venasakulchai, Anan.venasakulchai@gpo-mbp.com
Inspected site	
Address of inspected manufacturing site	241 Moo 7, Gateway City Industrial Estate Tambon Huasamrong, Amphoe Plaengyao, Chachoengsao 24190, Thailand GPS coordinates: DD: Latitude: 13.6157494, Longitude: 101.339135 DMS: Latitude: N 13° 26' 56.698", Longitude: 101° 20' 20.885".
Unit / block	Production JEV (formulation, filling, lyophilisation, capping, visual inspection, storage), Warehouse and Quality control laboratories.
Inspection details	
Dates of inspection	19 to 22 June 2018
Type of inspection	Routine inspection
Representative from the National Regulatory Authority	The national regulatory authority Thai FDA of the country was informed and representatives participated to the last day of the inspection.
Introduction	

Brief summary and general information about the manufacturing activities of the company	Government Pharmaceutical Organization - Merieux Biological Products Company Limited (GPO-MBP) was established by the Government Pharmaceutical Organization (GPO), Sanofi Pasteur and the Crown Property Bureau (Thailand) as a joint venture company. The GPO, a state enterprise, manufactures pharmaceutical products under the supervision of the Ministry of Public Health. Sanofi Pasteur, a French company, is a global pharmaceutical organization that supplies vaccines worldwide. The GPO-MBP manufacturing process is the downstream component whereby Sanofi Pasteur supply the bulk vaccine, and GPO-MBP formulate, sterile filter, fill, freeze dry, label, test and release the finished dosage forms. The site is located approximately 125km east of Bangkok, with the site comprising of seven buildings, employing approximately 130 staff.																												
History	The regulatory inspections history of the company is summarized in the table below: <table><tr><td rowspan="13"> Thai FDA  สำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข </td><td>October 2002</td><td rowspan="3"> WHO  World Health Organization </td><td>June 2009 (Measles)</td></tr><tr><td>October 2003</td><td rowspan="2">14-19 May 2014 (IMOJEV MD)</td></tr><tr><td>June 2006</td></tr><tr><td>August 2007</td><td rowspan="5"> TGA (Australia)  Australian Government Department of Health Therapeutic Goods Administrations </td><td>May 2008</td></tr><tr><td>May 2008</td><td>December 2010</td></tr><tr><td>June 2009</td><td>July 2012</td></tr><tr><td>April 2010</td><td>October 2015</td></tr><tr><td>March 2012</td></tr><tr><td>February 2013</td><td rowspan="3"> South Korea MFDS </td><td>August 2014</td></tr><tr><td>August 2014</td><td rowspan="2"> BPOM Indonesia </td><td>October 2014</td></tr><tr><td>October 2015</td><td rowspan="2"> Taiwan FDA </td><td>28 – 30 March 2016</td></tr><tr><td>18 – 20 January 2016</td></tr><tr><td>04 – 07 September 2017</td></tr></table>	Thai FDA  สำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข	October 2002	WHO  World Health Organization	June 2009 (Measles)	October 2003	14-19 May 2014 (IMOJEV MD)	June 2006	August 2007	TGA (Australia)  Australian Government Department of Health Therapeutic Goods Administrations	May 2008	May 2008	December 2010	June 2009	July 2012	April 2010	October 2015	March 2012	February 2013	South Korea MFDS	August 2014	August 2014	BPOM Indonesia	October 2014	October 2015	Taiwan FDA	28 – 30 March 2016	18 – 20 January 2016	04 – 07 September 2017
Thai FDA  สำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุข	October 2002		WHO  World Health Organization		June 2009 (Measles)																								
	October 2003				14-19 May 2014 (IMOJEV MD)																								
	June 2006																												
	August 2007		TGA (Australia)  Australian Government Department of Health Therapeutic Goods Administrations	May 2008																									
	May 2008			December 2010																									
	June 2009			July 2012																									
	April 2010			October 2015																									
	March 2012																												
	February 2013		South Korea MFDS	August 2014																									
	August 2014			BPOM Indonesia	October 2014																								
	October 2015				Taiwan FDA	28 – 30 March 2016																							
	18 – 20 January 2016																												
	04 – 07 September 2017																												
Brief report of inspection activities undertaken																													
Scope and limitations																													
Areas inspected	The inspection focused on the production and control of Japanese Encephalitis Vaccine (live, attenuated). The inspection covered the sections of the WHO GMP text, including quality assurance, sanitization and hygiene, complaints and recalls, self-inspection, personnel, training, personal hygiene, premises and equipment, materials, documentation, qualification and validation, production, quality control and utilities.																												
Restrictions	None																												
Out of scope	Products and vaccines other than Japanese Encephalitis vaccine (live, attenuated) were not inspected during this inspection.																												
Vaccines covered by the	Japanese Encephalitis Vaccine (live, attenuated), JEV 4 dose presentation.																												

inspection	Lyophilised active component to be reconstituted with diluent before use. Two vial set (active + excipient) Diluent Solution of sodium chloride 0.9%.
------------	---

Abbreviations	AEFI	Adverse Event Following Immunization
	AHU	Air Handling Unit
	ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
	APR	Annual Product Review
	APS	Aseptic Process Simulation
	BMR	Batch Manufacturing Record
	BPR	Batch Production Record
	CA	Compressed Air
	CAPA	Corrective Actions and Preventive Actions
	CC	Change Control
	CCIT	Container Closure Integrity Test
	CFU	Colony Forming Unit
	CIP	Cleaning In Place
	CoA	Certificate of Analysis
	CpK	Process capability
	DD	Decimal Degree
	DQ	Design Qualification
	DMS	Degrees, Minutes, Second
	DS	Drug substance
	EDI	Electronic Deionization
	EM	Environmental Monitoring
	FMEA	Failure Modes and Effects Analysis
	FTA	Fault Tree Analysis
	GMP	Good Manufacturing Practices
	GPT	Growth Promotion Test
	HEPA	High Efficiency Particulate Air
	HVAC	Heating, Ventilation and Air Conditioning
	IQ	Installation Qualification
	JE	Japanese Encephalitis
	JEV	Japanese Encephalitis Vaccine
	LAF	Laminar Air Flow
	MB	Microbiology
	MBL	Microbiology Laboratory
	MF	Master Formulae
	MFT	Media Fill Test
	MR	Management Review
	NCA	National Control Authority
	NCL	National Control Laboratory

NRA	National Regulatory Agency
OQ	Operational Qualification
PHA	Process Hazard Analysis
pH	(-ve) logarithm of H ⁺ concentration
PLC	Programmable Logic Controller
PM	Preventive Maintenance
PQ	Performance Qualification
PQR	Product Quality Review
PQS	Pharmaceutical Quality System
PSUR	Periodic Safety Update Reports
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
QMS	Quality Management System
QRM	Quality Risk Management
QTA	Quality Technical Agreement
RA	Risk Assessment
RCA	Root Cause Analysis
RO	Reverse Osmosis
SIP	Sterilization In Place
SMF	Site Master File
SOP	Standard Operating Procedure
SP	Sanofi Pasteur
TOR	Time Out of Refrigerator (2°C to 8°C)
UN	United Nations
UNICEF	United Nations Children's Fund
URS	User Requirements Specifications
UV	Ultraviolet-Visible Spectrophotometer
VVM	Vaccine Vial Monitor
WFI	Water for Injection
WHO	World Health Organization

Part 2: Brief summary of the findings and comments**1. Pharmaceutical quality system**

The quality management system of GPO-MBP was established with adequate and trained staff. The organization charts of the departments were available with the staff assigned to their functions within the organization. The quality management system and the quality control activities were independent of the production unit. The quality commitment of the company was ensured through the principles of quality risk management and continual improvement. There were standard operating procedures for the key activities including the product quality review and the quality risk management. The staff received regular training on the principles of GMP. The job descriptions of the head of quality assurance and regulatory affairs, quality control and production were spot checked and found to be adequate.

In general the current Pharmaceutical quality system and all of the elements were in place however these elements varied in their maturity and some needed further attention and improvement.

The company had adequately addressed the deficiencies related to the QMS, PQR and QRM through the CAPA.

Product Quality Review:

The JE-CV were manufactured by GPO-MBP under the product ownership of Sanofi Pasteur. The shelf life of the JE-CV vaccine and the diluent were 3 years respectively.

Sanofi Pasteur Biologics LLC, USA was the supplier of JE-CV concentrated bulks for the production at GPO-MBP. The imported concentrated bulk of vaccine was formulated, online sterile filtered, filled, lyophilized, controlled and released for sale by GPO-MBP. Provision was in place to provide GPO-MBP with relevant data of the PQR reports in a timely manner. The annual product review summary report JE – CV approved in May 2014 was available. There were three lots produced and released to market from 29 October 2011 until 25 October 2012. No other batch was produced since then.

The procedure for product quality review was in place. JE vaccine was processed in multiple sites and released at GPO-MBP.

The company's PQR approach was generally in line with WHO requirements however a number of elements were not specifically called for in the PQR.

The PQR JE-Chimeric vaccine (JE-CV)) was spot checked. The review period covered was from August 2016 to July 2017. One dose and four dose presentations were developed using the same 3 mL vial. The formulation of 4 dose presentation was calculated as five times of 1 dose concentration ensuring that when the vaccine is reconstituted with 2.6 mL of diluent, at least 4 doses of JE-CV vaccine could be extracted from the vial. The specifications of 1 dose and 4 dose presentations were comparable with the only exception of osmolality. The fill volume is 0.5 mL. There were two types of diluent for JE-CV vaccine: 0.4% NaCl solution for 1 dose presentation and 0.9% for 4 dose presentation.

During the review period, 37 lots of JE-CV vaccines with 1 dose and 4 lots of JE-CV vaccines with 4 dose presentation were produced. No rejection, reworking or reprocessing was reported for JE-CV vaccines since 2015. 1 lot of diluent for 1 dose presentation was rejected in 2015. 1 lot of diluent for 4 dose presentation was rejected in 2015 and another lot rejected in 2016. The lot of diluent of 4 dose presentation was rejected due to OOS of sodium chloride content. The formulation of one lot of diluent was stopped because the related part of the batch record was missing.

The review of critical in-process parameters included lyophilisation, online sterilisation, terminal steam sterilisation of diluent in addition to the yield analysis, percentage of defects in visual inspection, time out of refrigerator, stirring during formulation and capability of filled volume.

For visual inspection, one JE-CV vaccine lot had high visual inspection rejection rate of 8.96% due to defective fill volume. One diluent lot had high visual inspection rejection rate of 5.35% due to black stain found on the aluminum caps during capping process.

Process capability of filled volume for all batches and diluent was greater than 1.

One deviation related to the malfunction of the freeze drier that occurred during lyophilizing process was spot checked. The product impact was reviewed and some additional tests were performed before confirming this event had not quality impact on the concerned lot number of 1 dose JE-CV.

The review of results of release data and critical in-process controls data was spot checked. All the results presented were within the established specifications. This included for 4 dose presentation the appearance before and after reconstitution, the reconstitution time (nmt 3 min), the pH, the osmolality (300 – 600 mOsm/kg against 400 – 900 mOsm/kg for 1 dose presentation), residual moisture (nmt 3%), sterility test, endotoxin test, identity by immunostaining, potency test, thermostability (7 days at 37 °C) and abnormal toxicity test (in mice and in guinea pigs).

The environmental monitoring test results were presented. The percentage of EM deviations per lot was 68% for JE-CV 1 dose and 75% for 4 dose presentations, 28% for diluent 1 dose and 38% for diluent for 4 dose presentation. The company mentioned that the deviations were investigated and closed appropriately without impact to the product quality. And additionally, corrective and preventive actions were identified.

The quality risk management:

The procedure for quality risk management was in place. Quality risk management reports were established by operational quality units, global quality supply chain and global quality risk management. The procedure covered entities of GPO-MBP in the development, laboratory studies, clinical studies management, manufacturing and distribution, inspection, regulatory submission and marketing throughout the lifecycle of the products. The document applied to the management of risks associated with quality and compliance. Other risks such as pharmacovigilance risk or risk to personnel were not within the scope of this document. The following tools were mentioned in the QRM procedure: FMEA, FMECA (Failure Mode, Effects, and Criticality Analysis), FTA, HACCP, HAZOP, PHA (Preliminary Hazard Analysis), Ishikawa (6M) and 5 Why.

Deviation management:

The procedure for the management of deviations was in place. Unplanned activities were managed through the deviation control system. There was a system of root cause analysis and information to the relevant department.

Management review:

There existed a procedure for the management review meetings which takes place once a year. There was also GPO-MBP site quality council chaired by the managing director and attended by the senior management which deals directly with the quality related issues. All the site related quality problems were reviewed by the site quality council and senior management team is supported by the Sanofi Pasteur head of regional quality.

Change control:

The procedure for the change control was reviewed. There existed the categorization of the changes into minor, major and critical changes. The procedure applied to all the GMP related changes.

CAPA management:

The procedure for the CAPA management was reviewed. The CAPAs from the complaints, deviations, and self-inspection were addressed as per this procedure. The risk based approach was referred to in the guidance and the procedure included the CAPA determination matrix based on the severity of deviation and likelihood of the event with the same root cause. The procedure also had the provision for the continuous improvement. The decision to implement the CAPA was defined in the relevant procedure which is the responsibility of the functional area and the quality representative.

The CAPAs from the last inspection of WHO in 2014 were reviewed and most of the CAPAs were found to be closed as per the proposed timelines except in two cases. One CAPA was found to be not closed and one CAPA was partially closed. The implementation of CAPA was found to be weak in terms of the root cause analysis and timely implementation. For example, the company has installed horizontal airflow in the loading area of the stoppered lyophilized vials however the training of the staff in the aseptic area was found to be insufficiently documented.

Though the company could demonstrate the timely implementation of most of the CAPAs, The root cause analysis was found to be insufficient in case of the vial micro leakage recorded in the year 2015 several times.

Documentation:

Overall, the document management system was governed by through the relevant procedures. The list of the procedures was found to cover all the activities.

Batch Release Process:

The batch release process was in place through relevant procedures. Quality assurance manager was assigned to review batch production record for all the product and raw material used for manufacturing of the finished products. There was no data available for the rejected batches of the finished products. The release for sale of products was done after lot release by the local authority.

Batch Manufacturing Record:

The BMRs were found to be maintained as per the requirements in place. The batch manufacturing record of one lot of JEV was spot checked and the page 28 of this BMR was found deficient in not mentioning the critical step of final filtration before filling.

The following documents were spot checked

- Procedure for archiving, retrieval and record retention of GMP records,
- The test control procedures for JEV,
- The certificate of analysis for the drug product was issued by QA,
- SOP for batch numbering system. The coding of product lot number was found weak in not having the specific batch numbers for the trial batches,
- The list of stability studies for JEV and diluent. GPO conducted the real time and accelerated stability for the multidose vial and the diluent. The proposal for the conduct of the stability studies for the formulation with the extended shelf life of the bulk from 5 years to 7 years was spot checked. The company has planned for the stability study in June 2019 when the extended shelf life of the bulk will be implemented.

Lot Summary Product review:

The lot summary product review as per the relevant procedure was required for every lot of vaccine by the National Control Laboratory.

Self-inspection:

The procedure for the self-inspection was reviewed. The frequency of the self-inspection was decided based on the risk-based approach. A lead inspector was selected after approval by the QA. The self-inspection was considered adequately implemented in terms of reporting the CAPAs to the concerned division and the root cause analysis.

Contract production, analysis and other activities And Quality agreement:

The quality agreement for the manufacturing services described the responsibilities and obligations of the parties with regards to the manufacturing operations. As per this agreement GPO-MBP shall not subcontract any work related to manufacturing operations without the prior written approval of Sanofi Pasteur. The quality agreement defined the roles of the GPO-MBP and Sanofi Pasteur but in certain areas the role was not clear.

Personnel:

GPO-MBP has 130 employees and the organization charts of all the departments was spot checked and found to be adequately defined with the qualified and trained staff.

Department	Number of Employees
Managing Director, Deputy Managing Director and Office Manager	03
Production	49
Quality assurance and Regulatory affairs	09
Quality Control	22
Engineering and Maintenance	18
Material Management	09
Manufacturing Technology	02
Finance and Account	05
Health, safety and Environment	05
Human Resource and site service	08
Total	130

The job descriptions for the staff were spot checked. There were eight aseptic operators and the job descriptions for these operators were reviewed. There was a procedure which describes the number of aseptic operators to be inside grade A area and the supporting grade B area but the access control of these aseptic operators to the aseptic area at a particular time could not be demonstrated by the company.

Training:

The training records of the personnel were maintained in the electronic form. The training records of the aseptic operators were spot checked. The operators undergo aseptic operations training twice a year. Training provided to one of the operators was found not updated.

It was observed that the trainings provided were in-house. It would be recommended to have more comprehensive trainings for GMP. An example of insufficient training of the staff responsible for the the quality risk management was raised as detailed in the section above.

Personal hygiene:

The records for the personal hygiene were found to be maintained for all the employees. All the employees were required to undergo a complete health check-up at the time of recruitment. The company has a well-established vaccination policy for the employees and the vaccination records for the employees in the critical areas of operation were spot checked and found to be satisfactory.

Complaints:

The SOP for management of complaints was reviewed. The complaints for internationally shipped products were received by Sanofi Pasteur, the marketing authorization holder and forwarded to GPO-MBP. The complaints related to damage to secondary carton during transport were spot checked and found to be adequately documented.

One complaint related to the presence of a substance difficult to dissolve in the vaccine vial was reviewed. The complaint was supported by the photograph only and the sample was not found returned by the complainant. The investigation included testing on the retention samples of the same batch and no defect was recorded. No recurrence or similar complaints regarding a substance difficult to dissolve was recorded. The complaint was closed and no subsequent follow-up by the complainant was recorded.

Product recalls:

The procedure for managing the recall was reviewed. The last mock recall dated October 2018 was reviewed which depicted an incorrect expiry date indicated on the product for a JEV batch delivered to market. Report included inventory on product distributed and also a copy of the rapid quality notification (generated by GPO-MBP staff using SP on-line system) which would be sent to the SP company representative in the recipient country. The report was found deficient in not having any record of the letter being sent to Sanofi Pasteur and data on the stock status in the mock recall.

The dual responsibility of Sanofi Pasteur, the marketing authorization holder, and GPO-MBP were not defined clearly as the role of GPO MBP was found to be limited to notification to the regional staff of Sanofi Pasteur.

Pharmacovigilance:

The procedure for the management of the AEFI was reviewed. Sanofi Pasteur was responsible for maintaining and providing yearly summary for the products manufactured in other countries. GPO-MBP was responsible for collection of data in case of the products marketed in Thailand only. The reports of incorrect administration of the multidose JEV to single recipients were reviewed and found to be deficient in not being followed up for the reported adverse events. There were no reports of AEFI from Myanmar and Philippines for the JE vaccine multidose.

Sanofi Pasteur was responsible for the preparation of CIOMS and submission of PSUR to WHO/PQT in the annual report.

2. Production system

Virus seed lot system establishment, maintenance and testing; cell culture; production and control of single virus harvest; virus inoculation and incubation; harvest of vaccine virus; test on single harvest were all performed at US Sanofi Pasteur site in Canton, MA.

Drug substance was produced at that site in 2011-2012. Recently there was regulatory approval for an extension of shelf life of the DS to 7 years, based on 10 year real time data from DS batches used in clinical trials and manufactured in 2004 and statistical modelling from the available real time stability data of the commercial lots produced in 2011-2012. Subsequent real time data to 72 months was reviewed. The company indicated that further extension of shelf life of these batches was not planned and that two new batches of DS were manufactured in 2017.

This material was aliquoted and stored at -60°C. Since 2014, when the SAP management of warehouse started at GPO-MBP, material from only two lots of DS has been supplied. The DS was shipped on dry ice and there were two electronic temperature monitors (Temptale4) included. The state of the package and the temperature log were reviewed on arrival. A deviation report was reviewed concerning DS inspection lot (arrival in December 2017). It was noted that the expiry date on the outer container did not match with that of the inner container label and CoA. The deviation was sorted out in consultation with the QS at the canton site before the release of the drug substance for use. One container of DS received was sufficient for one lot of final product (multidose) or four lots of single dose. If the material was required for single dose vaccine lots, the material was thawed and divided into aliquots for future single dose batches and refrozen. A study demonstrating stability over two rounds of thawing was reviewed and considered satisfactory.

GPO-MBP accepted and released the DS based on CoA from Sanofi Pasteur, Canton and check of the label. In 2014 GPO-MBP introduced an identity test (plaque morphology immunostaining) which takes 7 days for the results. However, it was noted that the identity test was performed at the batch release of finished product.

Formulation of bulk in aseptic room was observed.

Connections were made in biosafety cabinets in a class B background. The final bulk tank was filled in the adjacent class C area via tubing through an access port from the formulation room. There was in line sterile filtration of the bulk. A sample batch manufacturing record reviewed indicated that filter integrity testing was performed before filter autoclaving; pre-use in place and after use.

During filling there was a second 0.22µm on line sterile filtration. The batch record included test results of pre-filtration bioburden.

Process validation reports from 2008 and 2011 (after introduction of the second sterile filtration during filling) were reviewed.

The initial validation report was performed in 2008. Another validation was performed in 2011 after the introduction of a filtration step on line during the aseptic filling. Pre and post filter virus titre and osmolality were checked and found within acceptance limits. The study also compared test results throughout filling process and demonstrated homogeneity of the batch. Batches produced with across specified range of stirring speed and time, were also demonstrated to be homogeneous. There was also no statistically different variation in results from samples within and between shelves of the lyophiliser (tested against all specifications including moisture content and reconstitution time).

This validation report did not include any testing of impact of variation in lyophilisation cycle on product to justify the parameters assigned. However, the company subsequently provided the report from product development by SP on establishment of the lyophilisation parameters. This was satisfactory.

The processing of multidose and single dose product was the same except for the required addition of concentrated DS. Calculations were indicated in the batch record. The bulk batch volume used reflected the lyophilizer capacity.

Following an observation at the last WHO inspection, the company modified the air supply to better protect the half stoppered vials by the mobile LAF used during unloading of the filling line and transfer to the lyophiliser. Loading and unloading of the lyophiliser were manual. The company project for lyophiliser replacement was discussed. The project has engaged the support of a consultant company. The project was in the purchase phase. The company planned shutdown of production from April 2019 till end of 2019.

There was stockpiling of vaccine, including diluent, to cover supply during the shutdown period. There will be a consequent relocation of the manual and semi-automatic visual inspection areas. The new lyophiliser specifications include compatibility with a further planned update of the filling line to use RABS technology.

Capping was not observed during the inspection period. Following an observation during the last WHO PQT inspection in 2014, the company has introduced an automated stoppering check before capping.

Due to limitations of space in cold room storage in production, space in warehouse cold room for finished product has been co-opted for this storage. There was a suitably segregated area for this and adequate security of samples. Unlabeled vials in trays were in boxes that were cable tie locked. Boxes were labelled and were on pallets with cling wrap surrounds. There was also pallet level labelling.

Observation was made of visual inspection (of JEV diluent) on 20 June. Additional segregation of reject vials that had been introduced as part of the CAPA following the 2014 inspection was observed. As noted previously, there were standard training and qualification vial sets maintained under adequate security in cold room. The last qualification and eyesight test of one operator observed on the day was reviewed. This was a new operator. She had to do 3 successful identifications with qualification kit and identify 100% of 25 defects in kit of 250. Up to four false positives were considered acceptable. (For annual requalification only one check of a qualification kit was required). After qualification, the operator performs inspection on real batches and these were 100% rechecked.

The company had adequately addressed the deficiencies related to the production through the CAPA.

3. Facilities and equipment system

GPO-MBP is located in clean surroundings and was dedicated facility for the manufacture of vaccine products. There was one production block with formulated bulk production area, filling and lyophilisation area, packaging area, warehouse, QC laboratory, utilities and offices. The animal house was located in a separate building. Overall, design and construction of the facility was acceptable. The facility was clean and kept in a good condition with a proper maintenance program.

The Site Master File has relevant documentation regarding the manufacturing processes, buildings, equipment, materials and personnel flows, utilities and maintenance plans.

Early formulation steps were carried out in Grade C area. Different laminar booths were available for dispensing of material, adding of starting material into the mixing tank and mixing and stirring in the mixing tank. Aseptic room was available for the first sterile filtration. Sterile bulk was kept in cold room after the first sterile filtration for a defined maximum hold time.

There was one filling line in grade A with grade B background. The final online sterile filtration was carried out in the grade B area. Performing PUPSIT and post-integrity of the sterilizing filter was the current practice at the company.

GPO-MBP being a multiproduct facility has dedicated equipment for formulation of different vaccines. The identification labels and specific placements were spot checked and found to be in order.

Production equipment were washed and sterilized in the washing area. There were two autoclaves available in the production area. One autoclave was used for both sterilization and decontamination of clothes and other equipment as well as for the sterilization of the diluent. The second autoclave was used for sterilization of filling equipment. After every use of autoclave for decontamination, a flushing cycle with an empty chamber run was conducted. The logbook was found to be adequately maintained.

The cloths of the operators were decontaminated on site then washed by third party supplier and sterilized at the site.

There were three cold rooms in the production area, used to store bulk product after each production steps. The cold room for the storage of vaccine in final container after capping and after visual inspection was inspected. It was maintained within the acceptable temperature limits. The temperature was monitored manually twice a day, and continuous monitoring records of temperature were also available and were reviewed every month. Segregation between non inspected and inspected vial available was spot checked and found acceptable. Color label was used to indicate status. Each batch of product was stored in a different pallet and wrapped with plastic to ensure its integrity.

Warehouse was access controlled, clean and supplied with adequate space and storage conditions. Pest control records were spot checked and found satisfactory. The storage provided good segregation between quarantine, release and reject. Quarantine and reject material have dedicated labelled and locked areas. Preprinted material and label was secure and kept in locked area.

There were two sampling areas. The sampling area for the sterile material was provided with the biosafety cabinet and was equipped with access rooms and having gowning provisions.

Cold store of finished product was visited. The most recent temperature validation (18-19 May, 2018) was reviewed and found satisfactory. Twelve calibrated temperature probes were used with their distribution indicated. Other than a spike in temperature at a location near the door (and indicated to be related to door opening), temperatures remained in established specifications. Two routine temperature monitoring points were located near temperature maximum points. The third routine monitoring point was near the door. There was no routine monitoring point near the coldest point identified during calibration.

➤ **Qualification and validation:**

Provisions for qualification and validation were found to be well defined in the Validation Master Plan and related study protocols. The most recent Validation Master Plan 2018 was reviewed.

The qualification and validation of the following equipment was spot checked.

- Aseptic process simulations,
- Lyophiliser,
- HVAC,
- Autoclaves,
- Depyrogenation tunnel,
- Fumigation of manufacturing facility,
- Cleaning and disinfection studies,
- PW and WFI,
- Environmental monitoring.

The company had adequately addressed the deficiencies related to the facility, equipment, validation and qualification through the CAPA.

4 Laboratory control system

The Quality Control was found to be independent from production and included a physiochemical testing laboratory, microbiology laboratory and sterility test room. The refrigerator for storing the samples was found to be temperature controlled through continuous monitoring and through manual recording twice daily. An alarm system for temperature was in place. Color coded stickers were used to differentiate samples to be tested, in testing process and approved samples. The reference standard for JE vaccine was found to be stored at -20°C with continuous temperature monitoring.

The list for the qualified analyst for performing each test was found to be maintained. Analytical report form was generated from the “Master Control Software”. Recent and outdated/ obsolete documents could be access through the application, but only recent document can be printed out.

All testing results were written manually and/or printed and signed manually, no electronic document was used.

➤ Management of OOS test results:

Handling of out of specification and out of trend test results (OOS and OOT) were conducted in accordance with the relevant procedure. When OOS occurred, preliminary investigation was initiated to confirm the event. Preliminary test included: check on analyst records, compliance to the testing procedure, correctness of calculation, check on the validity of material, reagent, test kit, reference standard, equipment, environmental conditions, sample preparation and storage, records, and similar documentation related to other batches. OOS was deemed invalid if the laboratory error was found. If no laboratory error was found, the investigation was extended to see whether there was problem in the production. Confirmed OOS could lead to batch rejection.

The procedure for trend management was established in 2017. The upper and lower limits were set based on the Mean-3 SD from the test results for the year 2016. OOT was raised if the upper or the lower limit was exceeded.

Provisional trend for control chart was made if the 15-30 data point was available. The trend for control chart will be finalized if more than 30 data point was available. Based on the provisional data chart, OOT can be issued.

List of OOS and OOT was spot checked and discussed in detail with the company.

Method Validation:

The validation of analytical method of potency and identity test for Chimeric JE Vaccine freeze dried product was conducted in 2007 and there was no change recorded since then.

The potency test method was based on the in house plaque assay. It was based on Vero cell culture, the reference standard material and four concentrations of the vaccine. Reference control used was a lot of JECV, manufactured by GPO-MBP and calibrated against the Thai National Central Laboratories.

5. Materials system

The material management of GPO-MBP involving handling of starting materials, packaging materials, bulk and finished products was reviewed. The company was found to maintain the list of approved suppliers as per the established specifications.

The warehouse was found to be well maintained in terms of the segregation of the material. The quarantine area was well maintained. There were dedicated areas for the sampling of the sterile material under the LAF. The area was shown to have adequate gowning procedure.

The report of the supplier audit of rubber stopper for the JE vaccine was spot checked. There exists a procedure for testing the integrity, identity, quality, quantity for all the starting materials.

The Warehouse has access controlled area for the storage of the bulk at the required temperature. There were three deep freezers with the dedicated freezer for the JE bulk as labeled at the time of inspection.

The rejected material was found to be segregated and the list of the material was provided. The list of critical materials was also spot checked and was found adequately maintained. Procedure for the rejected and returned material was found in order.

6. Packaging and labelling system

Labelling and packaging was performed in a dedicated area. Labelling of JEV single dose diluent was observed. Appropriate line clearance was performed and recorded. Label checks were taken for the batch record at the beginning and end of each roll of labels and when the foil was changed for printing of the batch specific data. There was good segregation of pre and post labelled material.

As observed at the last inspection, there was equipment available for VVM labelling if required. The last WHO/PQVAR received by WHO (in September 2017) indicated none had been supplied though the UN in the period covered by the report. There was a direct purchase of JEV MD by Philippines in October 2017 for outbreak response. It was indicated in the batch record reviewed that VVM was attached.

Packaging was observed for single dose JEV for which a vial of diluent and active, a syringe and two needles (for reconstitution and delivery). Since the last WHO inspection in 2014, the company has introduced an on-line automated photo checking of inner tray contents before cartoning with the product insert. The carton was then printed with the batch information. This equipment has capacity to add serialization coding information to the carton. To date, this was only required for deliveries to Republic of Korea.

For the MD presentation, there was separate cartoning of active and diluent. Each carton contains 10 vials of active or diluent. Twenty cartons were included in next level cartoning. Eighteen of these (=3600 vials, 14,400 doses) were packed into the insulated shipping box. Diluent was packed in the same type of box but cooling blocks were not included.

VVM:

The appropriateness of the choice for the VVM type (14) was adequately documented in the dossier submitted for prequalification and was not specifically reviewed further during the audit. Stability data examined was consistent with the VVM type. The incoming material testing of the VVM and the storage was considered appropriate.

Shipping Validation:

The shipping validation presented referenced the WHO International shipping guideline for vaccines but did not perform the validation according to those guidelines. It tested at ambient temperature of 2-8°C for 48h followed by ambient storage at 25°C with a requirement for vaccine to remain within 2-8°C for at least 6h at 25°C surrounding temperature. The report indicated maintenance of 2-8°C for at least 16h. A protocol was presented dated 14 June 2018 for a study to be conducted according to the shipping guideline in second half 2018. However, the inspector subsequently checked the dossier provided at the submission for PQ (2012) and

there was a report of a shipping validation performed according to the WHO guideline and meeting requirements, using “placebo vaccine”. The company subsequently explained that this was the reason they were planning to validate the shipping with JEV. However, the WHO Guidelines on the international packaging and shipping of vaccines (Annex 1) does not require the test to be repeated for each vaccine if the company can justify the similarity of presentation and packing of different vaccines.

Temperature monitoring:

Current shipments include a Temptale 4 electronic monitor with alarm set at 8°C. This device records every 30 minutes, after a 10 minutes delay, up to 40 days. Dedicated software and a reading device was required to access the data. There were no reported quality complaints of monitor alarm during transport. However, this device does not meet WHO prequalification specifications for a shipping indicator since it was not able to display the shipment’s time-temperature exposure without need for downloading to a PC and without need for a separate reading device.

http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=35

. To date, there has been no procurement of this vaccine through UN agencies. However, should such shipment occur, the temperature monitoring device used should be compliant with the above specifications.

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 the Corrective Actions taken and planned, and committed to be implemented, **GPO-MBP Co., Ltd. Thailand., 241 Moo 7, Gateway City Industrial Estate, Tambon Huasamrong, Amphoe Plaengyao, Chachoengsao 24190, Thailand** was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full inspection report as well as those reflected in the WHO Public Inspection Report (WHOPIR), were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

PART 4***List of GMP guidelines 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/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. 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/

3. 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

4. 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

5. 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/>

6. 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/>

7. 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

8. 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

9. 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

10. 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

11. 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

12. 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/

13. 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/

14. 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

15. 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

16. 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

17. 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

18. 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

- 19 Recommendations for Japanese encephalitis vaccine (inactivated) for human use (Revised 2007) for measles, mumps and rubella vaccines and combined vaccine (live).

Short name: *WHO TRS No. 963, Annex 1*

http://www.who.int/biologicals/vaccines/Annex_1_WHO_TRS_963.pdf?ua=1