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Prequalification Team Inspection Services
WHO PUBLIC INSPECTION REPORT
of the Vaccine Manufacturer

Part 1	**General information**
Manufacturer details	
Company information	
Name of manufacturer	**Japan BCG laboratory**.
Corporate address of manufacturer	Japan BCG Laboratory 1-5-21 Otsuka, Bunkyo-ku, Tokyo 112-0012, Japan
Contact person	Mr Satoshi Kodama Head of International Dept. JBL@bcg.gr.jp
Inspected site	
Address of inspected manufacturing site.	Japan BCG Laboratory, Kiyose Plant, 3-1-5, Matsuyama, Kiyose-shi, Tokyo, 204-0022, Japan
Unit / block	Building C (production of BCG in 2F and diluent in 1F); Building Z (visual inspection); Building M (packaging); Building DA (QC); Building D (Animal testing in 2F); Building I (storage); Building N (Shipping); Building A (QA).
Inspection details	
Dates of inspection	15 to 17 May 2019
Type of inspection	Follow up inspection. The previous inspection took place from 3 to 7 December 3 to 7, 2018, 2018.

Representative from the National Regulatory Authority	The national regulatory authority (PMDA) of Japan where the inspection took place was informed and participated to the inspection:
Introduction	
General information about the company and summary of the manufacturing activities	Japan BCG Laboratory was founded in 1952 as a separate entity from the Production Department of the Japan Anti-Tuberculosis Association (JATA). The intradermal BCG vaccine was exported since 1962 in collaboration with UNICEF. In 1966, WHO recognized the freeze-dried BCG vaccine from BCG Tokyo 172 strain as an international reference preparation of BCG vaccine. The current manufacturing facility of BCG vaccine "Building C" was built in 1992 and renovated in 2015. It is located in Kiyose plant in Tokyo Kiyose-shi. The list of the products manufactured at Japan BCG Laboratory are presented below: • Freeze-dried glutamate BCG vaccine for intradermal use, exclusively for export (this is the only prequalified vaccine); • Freeze-dried glutamate BCG vaccine for percutaneous use, mainly for domestic market and partly for export; • Immunobladder intravesical, mainly for domestic market and partly for export; • Freeze dried tuberculin, purified protein derivative, mainly for domestic market and partly for export; • In vitro diagnostic including: - Wellpack Medium S (kit for drug susceptibility test for mycobacteria, exclusively for domestic market); - QuantiFERON TB-Gold (Packaging of ELISA kit and blood collection tool).
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection focused on the production and control of the freeze-dried glutamate BCG vaccine for intradermal use. The inspection covered most of the sections of the WHO GMP text, including quality assurance, production, facility and equipment, quality control, material, labeling and packaging systems.
Restrictions	None
Out of scope	Products and vaccines other than freeze-dried glutamate BCG vaccine for intradermal use were not inspected during this inspection.
Vaccines covered by the inspection	Freeze dried Glutamate BCG vaccine in amber glass ampoules for intradermal use (10 or 20 doses). The diluent is Isotonic Sodium Solution in clear glass ampoules. 10 ampoules are packed in a corrugated ampoule holder and 10 holders (100 ampoules) are packed in the product box.

Abbreviations	AHU	Air Handling Unit
	ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
	APR	Annual Product Review
	APS	Aseptic Process Simulation
	BCG	Bacillus Calmette–Guérin
	BMR	Batch Manufacturing Record
	BPR	Batch Production Record
	CA	Compressed Air
	CAPA	Corrective Actions and Preventive Actions
	CC	Change Control
	CFU	Colony-Forming Unit
	CIP	Cleaning In Place
	CoA	Certificate of Analysis
	CpK	Process Capability
	DQ	Design Qualification
	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
	LAF	Laminar Air Flow
	LIMS	Laboratory Information Management System
	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
	MSG	Mono-Sodium L glutamate
	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

PSF	Product Summary File
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
QMS	Quality Management System
QRM	Quality Risk Management
RA	Risk Assessment
RCA	Root Cause Analysis
RO	Reverse Osmosis
SIP	Sterilization In Place
SMF	Site Master File
SOP	Standard Operating Procedure
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

There generally appeared to be adequate resources available for the management of the quality management system (QMS). Quality assurance and quality control activities were functioning with appropriate independence from the production unit.

Product quality review:

The WHO prequalified BCG vaccine for intradermal use is exclusively for export and not used in the domestic market. " Freeze-Dried BCG Vaccine (Percutaneous Use/Individual Use Only)" product is approved and marketed in Japan.

The APQR of the freeze-dried Glutamate BCG vaccines for 2018 was spot-checked.

The company had adequately addressed the issues raised through the CAPA plan.

CAPA management:

The procedure for management of the CAPAs was in place. Overall the CAPA can result from raised non-conformances, complaints, recalls, internal and regulatory inspections.

Documentation:

The procedure for computerized systems management was spot checked. The procedure for regulation of the control of log-book and the list of software were also presented.
The company policy was in line with the local regulation.

There was a company policy on IT information and security. There was a data integrity control procedure mentioning the principles of ALCOA principles, audit trail and that the data should be complete, consistent, enduring, available and reliable.

Batch release process:

The batch release process was addressed during the 2018 WHO Site Inspection for BCG vaccine.
In summary, the release process was laid down in the relevant procedure. The quality assurance department routinely initiates the batch release process. The required information is collected from the manufacturing control, inspection control and the quality control departments. The official batch release certificate from the National Institute of Infectious Diseases (NIID) should be issued for any lot of BCG vaccine before the release by the Quality Assurance manager.

The release process of one vaccine manufactured in 2018 was spot checked and found adequate.

Lot Summary Product (LSP) review:

The procedure for lot release process was spot checked.
The lot summary product for BCG vaccine was spot checked.

Self-inspection:
Three Self inspections were conducted in 2018 for QC (as per PIC/S check list) and production areas including hygiene aspects. The self-inspection report for production was spot checked. It was performed with two external consultants and internal auditors. The internal auditors had no specific training for auditing. The scope of the inspection was not mentioned. It was mentioned that the documentation review of randomly selected document lasted 2 hours. The report was barely limited to the finding. The resulting finding were managed by the CAPA owner and not followed up by the self-inspectors. There was no timeline in place for the CAPA to be provided by the auditees. These timelines were provided through the corrective actions to the finding. No records were in place for QA self-inspection and for self-inspection of self-inspection system. The risk assessment was not used to better plan self-inspection as per the priorities and criticalities. The company had addressed all the issues raised through the provided CAPA plan.

Contract production, analysis and other activities:
As part of vendor management, a new procedure was established. The document has identified the need for audits of Vendors/Labs which are providing service to the BCG manufacturer.
The qualification of the suppliers of the raw materials was in place as per the relevant procedure.

Personnel:
The company was adequately staffed. Sufficient number of employees engaged in the production, quality assurance, quality control, storage, engineering work section, shipping was provided.
Organizational charts showing relationships between different areas including Quality Assurance, production and Quality Control, with identification of the key personnel (head of production, QA, QC, warehousing, engineering) were provided. There was a clear separation between the quality control and production departments. Job descriptions of personnel were available. Qualification and job description of the quality control Manager was reviewed and found appropriate.

- ***Training:***

The basic and in-service training related to QA, QC and GMP were in place through a set of training procedures and records.

Specific training, curriculum and program were provided for QC personnel in area such as sterility tests, moist content, viability test, raw material and animal test. For example, for viability test the following program were indicated according to three levels:

- Level 1: Briefing was related to reading the procedure and the observation of the performance of the concerned technical step;
- Level 2: hands-on training, where the trainee should perform at least three training tests to be qualified. The manager did the assessment. Areas of involvement by the trainees include; sampling, inoculation and counting methods. The testing and reading of testing results by the trainee were conducted parallelly with qualified personnel.
- Level 3: It is a requirement that the testing of viability test should be repeated by the trainee at minimum 5 times.

The training record of an operator from QC area who was completed the viability and thermal stability tests was spot checked.

- ***Personal hygiene:***

Employees engaged in manufacture undergo medical checkups twice a year. Annual medical checkup includes a physical examination, chest X-ray and a consultation.

The person in charge of the manufacturing checks the health conditions of the employees engaged in manufacture and records the result in control records. The person in charge of hygienic control confirms that employees do not have their diseases or dangerous conditions that might damage the quality of the products.

2. Production system:

Good manufacturing practices generally were well implemented. Necessary resources were generally provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers, approved procedures and instructions, laboratories and equipment for in-process and other controls. Qualification and validation were routinely performed. Manufacturing steps were recorded in batch manufacturing record (BMR) and packaging records. Manufacturing processes were defined and reviewed. Deviations from procedures were recorded and investigated. Product was being released by the authorized persons of the Quality unit in accordance with written procedures.

The flow charts of the manufacturing processes of BCG vaccines along with the IPC, quality control tests, facility and equipment were provided in the SMF and PSF and discussed in detailed.

The following processes and procedure were reviewed in detail:

- Validation of Lyophilization Process:
- Vacuum check of temporary stoppered ampoules
- The manual visual inspection of freeze dried BCG vaccines.

3. Facilities and equipment system

The manufacturing building for BCG vaccine was dedicated. Zone segregation principles based on cleanliness grades were considered for premises. Production unit has individual HVAC systems, assuring the balance of pressure difference and air exchange frequency rates. Pressure differentials between the premises with different cleanliness grade were provided. Regular environmental monitoring was carried out. Cleaning and disinfection of premises and equipment were in place. Regarding the bio-waste management, procedures for discarding wastes in production area have been spot-checked and found adequate.

The company provided the SMF and the PSF with relevant documentation regarding the manufacturing processes, buildings, equipment, materials and personnel flows, utilities and maintenance plans.

Introductory session was provided on primary, secondary and tertiary gowning for entry to the production area Building C, Filling process of BCG vaccine. Gowning procedure of operators and access to the production area are provided in procedure for Gowning.

The normal practice of dressing the secondary gowning to enter the classified D Grade Area occurred in the clean non-classified (CNC) Area.

The filling process was watched through a monitor located in classified Grade D.

➢ ***Qualification and validation***

Provisions for qualification and validation were in place and cover premises, equipment, utilities and systems, processes and procedures at periodic intervals and when changes have been made. Preventive maintenance programme and calibration plan were in place.

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

- Validation of aseptic process through media simulations;
- Validation of the homogenization of the product;
- Validation of viable counts in the potency assay;
- Qualification of the spectro-densitometer:
- HVAC qualification;
- Autoclaves (steam sterilization of the diluents, media and material of the filling machine);
- Lyophilizer;
- Cleaning and disinfection studies;
- Incubators;
- Water and pure steam.

4. Laboratory control system

Quality Control was an independent department, separate from the Production. QC performs testing of incoming raw materials, packing materials, intermediate products, final and finished products, as well as the environmental monitoring and stability studies for intermediate / finished products. Animal testing is also carried out by Quality Control Department. The products at intermediate/final stages are tested against established specifications as per respective testing SOPs.

5 Materials system

Overall, provisions for incoming materials, intermediates and finished products were in place for reception, quarantine and release processes. Appropriate storage conditions were provided. Rejected and returned material procedures were in place.

6 Packaging and labelling system and International shipping

VVM storage, labelling, and packaging took place in level two of building M. VVM were stored in two freezers. The VVM need to be kept in cold conditions and protected from light. Upon reception, the presence of remaining dry ice in the packaging is checked and the VVM are transferred to the freezer and locked by QC staff during the testing period. The status of the VVM was affixed on the door of the freezer. The release testing process takes about 1 month. Once released, the freezer is unlocked and the VVM becomes available to production. A new status tag is affixed accordingly, including the expiry date of the VVM.

Packaging procedures for international shipment was observed during the site visit. The area was well organized, tidy and clean. The 2 - 8°C cold room was visited which is designated for UNICEF vaccine orders. The room temperature was monitored with several temperature probes. There was a BCG vaccine lot ready for dispatching. The shipment contains a total of 4 boxes of 10 boxes which each contains 100 ampoules per product box. The vaccine shipment was packed in insulated polystyrene type container surrounded by 10 ice packs. The shipment was supplied with a temperature monitor Q-tag type 2.
The company was following the WHO Guidelines on international packaging Class B packaging requirement (WHO IVB 05.23) for international shipping validation; The vaccines must be packed to

ensure that the warmest temperature inside the insulated package does not rise above +30°C in continuous outside ambient temperatures of +43°C for a period of at least 48 hours.

Three independent runs of the study were performed using several sensors placed at different locations in the full load at ambient temperature of +43°C. The study results revealed that the minimum and maximum temperatures from 3 runs met the acceptance criteria established by WHO guideline WHO/IVB/05.23.

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, **Japan BCG laboratory**, located at **Kiyose Plant, 3-1-5, Matsuyama, Kiyose-shi, Tokyo, 204-0022, Japan**, 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.

DEFINITIONS

Critical deficiency
A *critical* deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

Major deficiency
A *major* deficiency may be defined as a non-critical observation that:

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

Other deficiency
A deficiency may be classified as other if it cannot be classified as either critical or major, but indicates a departure from GMP. A deficiency may be other either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as major.

PART 5

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-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: 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/

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. 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

18. 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

19. Recommendations to assure the quality, safety and efficacy of BCG vaccines
World Health Organization, 2013 (WHO Technical Report Series No. 979), Annex 3.
Short name: WHO TRS No. 979, Annex 3.
https://www.who.int/biologicals/areas/vaccines/TRS_979_Annex_3.pdf?ua=1