**Prequalification Team**  
**WHO PUBLIC INSPECTION REPORT**  
**Vaccines Manufacturer**

## Part 1: General information

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>Janssen Vaccines (Berna Biotech Korea Corp)</th>
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<tbody>
<tr>
<td>Contact person and email address</td>
<td>Dr Lodewijk Venhuizen, <a href="mailto:lvenhuiz@its.jnj.com">lvenhuiz@its.jnj.com</a></td>
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<tr>
<td>Date of inspection</td>
<td>13 to 17 June 2016</td>
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<tr>
<td>Type of inspection</td>
<td>Routine GMP inspection</td>
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<tr>
<td>Dosage forms(s) included in the inspection</td>
<td>Injectable</td>
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</table>

**WHO product numbers covered by the inspection**

- Diphtheria-Tetanus-Pertussis (whole cell), Hepatitis B, Haemophilus influenzae type b (Quinvaxem 1 dose).
- Diphtheria-Tetanus-Pertussis (whole cell), Hepatitis B, Haemophilus influenzae type b multidose (Quinvaxem MDV 5 and 10 dose).
- Hepatitis B (Hepavax 10 dose).
- Hepatitis B (Hepavax gene TF 1 dose).

**Summary of the activities performed by the manufacturer**

Manufacturing of drug substance, formulation and filling, quality controls, warehousing and shipping.
PART 2: SUMMARY

General information about the company and site
Janssen Vaccines Corp is an international pharmaceutical company striving to provide worldwide access to prophylactic vaccines that are of high quality, safe and affordable. All corporate activities are dedicated to development, production and the worldwide distribution of vaccines.

Green Cross Vaccine Corp. (the present Janssen Vaccines Corp.) was incorporated in 1999 as a subsidiary of Korea Green Cross Corp., a pioneer in the vaccine field since 1967. In 2000, the Dutch group, Rhein Biotech acquired the majority of Green Cross Vaccine Corp. shares. In 2002, Green Cross Vaccine Corp. became a member of the Berna Biotech Group with crucial responsibilities in production, research & development and sales & marketing activities. In February 2006, Crucell acquired Berna Biotech to become the leading independent vaccine company. Berna Biotech’s state of the art respiratory, paediatric and travel vaccines have put Crucell even more at the forefront of fighting infectious and other diseases. In May 2006, the company name, Green Cross Vaccine Corp. was changed to Berna Biotech Korea Corp. (BBKC). In 2011, the manufacturing site was relocated from Shingal to Incheon. Johnson & Johnson completed the tender offer for Crucell, headquarters of Berna Biotech Korea, on 22nd February 2011 and declared the offer unconditional. As a result, Crucell became one of the Janssen Pharmaceutical Companies of Johnson & Johnson. On January 6th, 2016, the legal entity name in the business license has been changed from Berna Biotech Korea Corp. to Janssen Vaccines Corp. Hereafter, Janssen Vaccines Corp advised WHO of the change in company name and consequent branding of the currently WHO prequalified vaccines.

Incheon Site located at Songdo, in the Incheon Free-Economic Zone (IFEZ), 30 km southeast of the Incheon (Seoul) international airport was established in May 2010. The site is surrounded by academic area and industrial area. The area of the site is approximately 33,500 m² and building area is approximately 19,300 m². The products manufactured at the site are vaccines for human use.

BBKC pharmaceutical manufacturing license (License date: November 9, 1999), License No. 2091 (former 709) was issued by Korean Ministry of Food & Drug Safety (MFDS).

History of WHO and/or regulatory agency inspections
The following list of inspections took place at the above mentioned site:

- Routine GMP inspection by MFDS, Korea 21-24.12.2010;
- Pre-approval Inspection for Quinvaxem® inj. produced in a new manufacturing site, Incheon site by MFDS 12-15, 18-19.07.2011;
- Routine GMP Inspection for Biological Product Importers by MFDS 18.11.2011;
- Routine GMP Inspection by MFDS 06-09.03.2012;
- Routine GMP Inspection of Hepavax-Gene® TF inj. By Polish Main Pharmaceutical Inspectorate 13-16.03.2012;
- Routine GMP Inspection for Hepavax-Gene® TF inj. and Quinvaxem® inj. by National Institute for the Surveillance of Drug and Food, Colombia 19-22.03.2012;
This inspection report is the property of the WHO
Contact: prequalinspection@who.int

GMP Inspection for Hepatitis B vaccine bulk, NADFC, Indonesia (NADFC: National Agency of Drug and Food Control) 02-05.04.2012;
Pre-approval Inspection for Quinvaxem® inj. by NADFC, Indonesia (NADFC: National Agency of Drug and Food Control) 20-23.11.2012;
GMP Inspection for Quinvaxem® inj. by MFDS 07-09.05.2013;
Renewal of Quinvaxem® inj. by MoPH, Republic of Kazakhstan (MoPH: Minister of Public Health) 01-04.07.2013;
Routine Inspection for Animal facilities by MFDS 09.07.2013;
Registration of Quinvaxem® inj. by SFDA, Saudi Arabia (SFDA: Saudi Food and Drug Authority) 03-05.09.2013;
Pre-approval Inspection for Quinvaxem® in cPAD by MFDS 8, 10-11.10.2013;
Routine GMP Inspection by MFDS 7-11.02.2014;
Routine Inspection for Animal facilities by MFDS 03.07.2014;
Routine GMP Inspection of Hepavax-Gene® TF inj. by Polish Main Pharmaceutical Inspectorate 03-06.02.2015;
Pre-approval Inspection for Quinvaxem® in MDV and Routine GMP Inspection by MFDS 13-17.04.2015.

**Focus of the inspection**
The inspection focused on the production and control of the following vaccines:
- Diphtheria-Tetanus-Pertussis (whole cell), Hepatitis B, *Haemophilus influenzae* type b (Quinvaxem 1 dose),
- Diphtheria-Tetanus-Pertussis (whole cell), Hepatitis B, *Haemophilus influenzae* type b multidose (Quinvaxem MDV 5 dose),
- Diphtheria-Tetanus-Pertussis (whole cell), Hepatitis B, *Haemophilus influenzae* type b multidose (Quinvaxem MDV 10 dose),
- Hepatitis B (Hepavax 10 dose),
- Hepatitis B (Hepavax gene TF 1 dose).
The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

**Inspected Areas**
- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Self-inspection
- Personnel
- Training
- Personal hygiene
PART 3: INSPECTION OUTCOME

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)
In general, the Pharmaceutical quality system and all of the elements was in place.

✓ Quality risk management
Provisions for Quality Risk management were implemented. Examples of risk assessment was spot checked.

✓ Product quality review
The responsible QA Manager was in charge of initiating the Annual Product Review (APR) according to the implemented procedure. The APR was created in individual modules, whereby the data corresponding to the template for the module was compiled by the respective specialized department, for example by the Quality Control, Production, Compliance and/or other department. The consolidated APR was approved by the qualified person and the site quality head.

APR of Quinvaxem® inj. (Diphtheria-Tetanus-Whole Cell Pertussis-Hepatitis B (rDNA)-Haemophilus influenzae type b conjugated to Diphtheria CRM197, Combination Vaccine (DTwP-HepB-Hib Fully Liquid Combination Vaccine) covering the manufacturing period from January to December 2015 was spot checked.

12 final bulks and 41 finished batches were manufactured. One finished lot was rejected. According to the initiated deviation the wrong sterilisation recipe was used for the sterilisation of the rubber stoppers used for this lot.

During the filling, the 3rd exposed settle plate had 1 CFU identified as Bacillus megaterium. The part of the batch filled during the exposure of the 3rd settle plate onward was rejected.

No reprocessing was recorded and reworking was not allowed according to the company.

Green Cross Corporation was a CMO for filling. However, no activities related to this product have occurred there since 2013.

The active substances are provided by the manufacturing subcontractor. At reception only the identification test is carried out. The company rely on the test results in the certificate of analysis to continue processing of these drug substances for formulation and aseptic filling.

Quinvaxem® MDV: so far, only one batch of final bulk was manufactured on 17 April 2016 and two batches of 10 dose (5mL/vial) manufactured on 19 and 20 April 2016 respectively.

The following APR were spot checked:
• Annual product review / product quality review for Hepatitis B Vaccine (rDNA) Final Aqueous bulk (Thiomersal free), Review period 01/01/2015 to 31/12/2015.

• Annual product review / product quality review for Hepatitis B Vaccine (rDNA) Final Aqueous bulk (Thiomersal), review period 01/01/2015 to 31/12/2015.

• Annual product review / product quality review for Hepatitis B Vaccine (rDNA) Final Product. Both Thiomersal Containing (6 filling lots produced) and Thiomersal free (9 filling lots)

In general terms the APR management showed weaknesses and deficiencies were accordingly raised during the inspection. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the Annual Product Quality Reviews.

✓ Change Control management
Provisions for change control handling were in place. The change control scope covers all manufacturing activities and suppliers that may have an impact to the quality of the product. Changes were categorised as high and low. Change controls categorised as high include those having an impact related to regulatory, marketing, quality, EHS and shortages. Change controls categorised as low have no regulatory impact and do not have significant quality impact.

The list of change controls initiated since 2014 was spot checked.

✓ Deviation
Provisions for deviation management were implemented. Examples of deviations and investigations were spot checked.

✓ CAPA management
Provisions for CAPA handling were in place. The list of CAPAs since 2014 was spot checked. Most of the CAPAs created before March 2016 are considered as closed or complete. After March 2016, CAPAs have the record state of closed, awaiting closure review, pending closure, work in progress.

The last MFDS inspection took place from 13 to 17 April 2015 for the approval of Quinvaxem MDV. All raised deficiencies were considered adequately addressed by the MFDS and the corresponding CAPAs were closed.

Event, deviation and CAPA are managed by the quality management software (EQMS) Trackwise®.
Batch release
The batch release by the manufacturer was performed according to approved procedures. The MFDS approval of lots meant for export was based on protocol review.

3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS
The level of implementation of good manufacturing practices was considered satisfactory. In general terms, resources were available, including qualified and trained personnel, premises, equipment and services, materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing processes were defined. Instructions and procedures were available. Qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Operators were trained to carry out procedures, and records were made for production. Key elements of GMP were available however additional efforts were required to be in full compliance with WHO good manufacturing practices and guidelines. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the good manufacturing practices.

3.3 SANITATION AND HYGIENE
The premises were maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines were not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewellery were not observed as being worn in clean areas. Manufacturing areas are provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified and contained manufacturing areas were in place. Changing rooms were provided with photos describing the gowning procedures. During the inspection the gowning procedures appeared to be complied with and no dress code violations noted. The level of hygiene observed and the measures taken to maintain this were considered satisfactory.

3.4 QUALIFICATION AND VALIDATION
A Validation Master Plan was available and describes the validation and qualification process for equipment and method for manufacturing and quality control activities. The qualification status of the equipment was managed through the document “Qualification status and schedules as well as the planning of qualification activities. Qualification reports were spot checked as listed below. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the qualification and the validation.

Regarding the qualification of the cold room and the warehouse it was recommended to take into consideration the information regarding homogeneity, stability, error of measurement.
✓ Process validation
Process validation was performed at 3 year intervals or with respect to a change in process. The process validation report of Hepavax TF performed in 2015 was spot checked and considered satisfactory.

✓ Air flow pattern
Data of airflow pattern at static and dynamic conditions were available for the filling machine. Data on airflow pattern in static conditions were available for the formulation area of grade A within grade B background. The airflow pattern at dynamic conditions for the formulation process was not considered.

✓ Integrity of containers
Aluminium phosphate solution was stored in polypropylene bottles of 50 L. Diphtheria drug substance was stored in Glass bottles of 5L. Tetanus toxoid drug substance was stored in glass bottles of 5L. Whole cell pertussis drug substance was stored in glass bottle of 20L. CRM197-Hib drug substance was stored in 1L of plastic bottles. Container types for the drug substances supply was specified in the contract between Janssen and the manufacturing subcontractor. An executive summary supporting a conclusive Container Closure Integrity Test (CCIT) data on the above mentioned containers from the supplier was available. This was performed via growth media stored in similar representative containers for up to the maximum storage period and showed no microbial growth.

For CRM197-Hib drug substance up to 10 containers of around 600 mL were pooled in a stainless steel tank equipped with aseptic connectors and tubing for aseptic transfer and stored up to seven days in the cold room claimed as grade C at 2 to 8°C. Diphtheria drug substance was dispensed in 3 containers stored at 2 to 8°C for up to seven days. Tetanus Toxoid drug substance was dispensed in 3 containers stored at 2 to 8°C for up to seven days. The validation reports regarding the container closure integrity test and the holding storage time of pooled and dispensed drug substances were not available.

Formulated bulk was stored at 2 to 8 °C up to 7 days. Holding time storage period studies were carried out using growth media. Over pressure was applied on the formulated batch in formulation tank. The pressure in the tank was monitored over the holding storage period.

Disposable Ultra Low Density Polyethylene ULDPE single use bag of 100 L were used to store the formulated bulk of Quinvaxem 1D at 2 to 8 °C for up to 12 months. The single use bags were filled from the stainless article formulation tank via aseptic connectors. The formulated bulk stored in the single use bags were pooled in the stainless steel formulation tank before the aseptic filling. Data on extractible analysis Flexboy Bags from the supplier were available. The protocol entitled “Validation of S40 bags with regard to leachable with a vaccine solution Quinvaxem from Berna Biotech Korea Corp” with applicable date of 2009/02/02 from the supplier was available. The final report (T-12 months): leachable study between Flexel bags (S40) and Quinvaxem for Berna Biotech with applicable date of 2010/05/28 was available.
The data package regarding leachable and extractible was not provided during licensing submission for review by the competent authority neither in the submitted PSF for review during the prequalification process.

✔ Media simulation test
Provisions for aseptic process simulation were in place. Soy Bean Casein Digest Media was used in the aseptic simulation and filled units were incubated at 20-25°C for 7 days, visually inspected and transferred for incubation at 30-35°C and visually inspected after 7 days. Samples were drawn for Growth Promotion Test including the beginning and the end of the aseptic simulation process. In addition to the recommended strains in pharmacopoeial monograph, as in house isolate flora was used.

The manual process simulations including the pooling and the distribution of the drug substances for the formulation preparations were simulated considering the maximum number and transfer time of aseptic operations as well as the maximum volume of the drug substances as used in the routine process.

Aseptic process simulations of formulation, filling and subdivisions were performed for most of the aseptic operations except for the transfer of the formulated bulk from single use bags to the formulation tank.

The list of the aseptic media simulations carried out since the initial validation in 2010 was presented. Aseptic operators participate in the aseptic media simulation at least once a year.

The media fill test (in 2012) was invalid, this was related to the air filter integrity failure of the recirculation tank of 300L.

The media fill test (in 2012) was invalid, this was related to the single use bag that was leaking.

✔ Dry Heat Tunnel Sterilizer
Periodic requalification was performed annually. Instrument calibration system, verification of system configuration, validation equipment calibration verification, HEPA filter integrity test, air velocity test, air borne particle test, loaded chamber heat penetration test and endotoxin challenge test were considered. The last requalification was performed in October 2015. After preventive maintenance cleaning and disinfection were performed in the cooling area and sampling for settle plate, swab and particles as grade A specification was performed. Air borne particle test was not performed on the preheating filter.

✔ Formulation suite’s autoclave
The re-qualification performed in June 2015 was spot checked. 5 pattern loads were re-qualified annually. According to the company the drying cycle and control of wet loads were considered in validation and routine process however this was not documented.

✔ CIP/SIP for filling material
Silicone tubing. The effect of the CIP/SIP on silicone tubing should be considered.

✔ QC equipment
Example equipment qualification spot checked was ELISA reader used for Hep B in vivo potency assay in QC. Annual qualification performed by equipment supplier was last

3.5 COMPLAINTS
Provisions for Complaints were in place. The investigation report on complaint is prepared by competent personnel and approved by Qualified Person (QP). Corrective actions are taken and preventive actions are considered to prevent recurrence of the issue. In case of serious or potentially life-threatening situation the MFDS and competent authorities are informed. Qualified person can decide to recall the corresponding batch of marketed product in accordance with SOP for recall.
The list of complaints from 2013 was spot checked.
Complaints records were reviewed monthly and review of recurrences was considered.

An example was reviewed where the company’s batch quality review associated with the receipt of an adverse event following immunisation and communication with Janssen global group responsible for Pharmacovigilance regarding this. This was considered suitable.

3.6 PRODUCT RECALLS
Recall was managed according to the implemented procedure. Recall was managed through Janssen global level group - The Quality Review Board. A Qualified Person from the Incheon site would be a member of this board for a product from this site or a product utilised in this country. An example of recall in China in 2016 based on mismatch of carton variable data (Hepavax TM batch 0.5mL) and barcode and vial label (Hepavax TM batch 1 mL). The management of this recall was adequately documented.

3.7 CONTRACT PRODUCTION AND ANALYSIS
The contract between Janssen and manufacturing subcontractor for supply of drug substances for Quinvaxem was reviewed. The manufacturing subcontractor has responsibility for quality control of this material and for provision of reference material related to these. The contract indicates that the manufacturing subcontractor should provide Product Quality Review (PQR) of the Drug Substances to Janssen. However, it was confirmed that Janssen did not have copies of these documents. The contract indicates that review of the PQR is one timing point which can permit review of the contract. The contract allows Janssen to conduct annual inspections to the manufacturing subcontractor facilities involved in Drug Substance manufacture. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the annual product quality review management.

3.8 SELF INSPECTION AND QUALITY AUDIT
Provision for Internal Audit was in place. The internal audit was conducted according to the SOP for Internal Audit to monitor the implementation and compliance with GMP principles and to propose necessary corrective measures. All GMP related areas were audited at least once a year.
Audit team members were qualified according to the SOP for internal Auditor Training and Qualification. Other internal or external experts can be selected as internal audit team members as needed.
Observations were raised during the audit and, where applicable, proposals for corrective actions and preventive actions (CAPAs), were reported to the management, leaders of designated teams and site Quality Head. Timelines were in place for CAPAs handling. The status of the CAPA follow-up was periodically monitored, evaluated and recorded. The annual audit schedule for internal audit 2016 and 2015 were available.

✓ Suppliers ‘audits and approval

Supplier were managed through the “Supplier selection and qualification” procedure that describes the process selection of a supplier, and through the Supplier monitoring procedure that describes the process of periodic assessment of the supplier.
A list of material was available and for each material a critical level was assigned (1 to 5). Each year through a “Proactive Source Quality System” performed during the first quarter and the next audit plan was defined for Critical level 1 to 4.
Audit could be performed by Berna Biotech Auditor or by J&J or JSC auditor team.
Frequency of audit was defined according to the critical level and can be adapted according to specific issue. The frequency was from one year to 6 years.
Supplier system management was in place and the following was recommended:
  - Set deadline for approval of the Johnson & Johnson / Janssen S Corporate audit reports.

3.9 PERSONNEL

Organization charts showing the arrangements for quality assurance, including production and quality control were provided by the company.
A training and qualification program was in place, which cover production and quality control.
The Training Management was described in the Standard Operating Procedure. A computerised system was used for the training.
Job descriptions were available for each personnel.
Qualification of visual inspection team was considered well planned and executed.
Every year, staff in charge of the visual inspection of the vials was re-qualified. This requalification was carried out using a test in which defective vials and non-defective vials were inspected. Staff must identify the defective vials and characterize the defects. The defective vials result from the rejections of production.
Training and qualification of aseptic operators and QC personnel performing sterility tests were in place and considered satisfactory.
3.10 PREMISES and Equipment

Simple floor plans including layout, air cleanliness classification and air flow of manufacturing and quality control areas were provided in the Site Master File as well as in the Product Summary File.

The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the premises and equipment as listed below.

✓ Storage areas

Warehouse was found to be cleaned and a well-organized state.

Quarantine, accepted and rejected products were stored on different and secured area. Products were correctly labelled according to their status.

Temperature was controlled and recorded. Labels of product were stored in the 1st floor of the warehouse in safety box secured through a computerised system.

A temperature qualification was periodically done (Periodic Re-Qualification for Warehouse February 2016)

Cold storage area for finished product was reviewed. This was three storey mesh floored facility with an electronic system with cage and pallet identification to manage stock, which was well segregated. Temperature mapping of the facility was performed annually and documentation of the most recent event that was spot checked and considered adequate.

Placement of routine sensors on each floor was based on identified hottest and coldest spots on each floor. Any movement of sensors was managed through documented system.

✓ Manufacturing areas

The monitoring of the differentials of pressures in the clean areas was described in the Standard Operating Procedure. This procedure describes the specifications of the differentials of pressures as well as specifications of alarm and action. The monitoring was performed through the Building Monitoring System.

✓ Filling line

The doors of the filling line under laminar air flow of grade A open into grade B area. The glass doors are equipped with gloves.

✓ Drug substance

When visiting the Hepavax DS production area, the room where clean tanks were stored was crowded with tanks which could present a risk to the staging and loading of the autoclave. The labels on these tanks indicated cleaning date. An SOP in the area indicated the expiry date after which new cleaning is required before use. It was subsequently indicated that this date can vary between items. This expiry date of the clean status was not recorded on the label.

Company representatives indicated their view that the situation was adequately controlled as it was necessary for an operator to record in the batch record the cleaning date and expiry date of equipment used. However, equipment in another part of the facility (larger fixed tanks) indicated both cleaning date and expiry date and adoption of this procedure for other tanks could reduce potential risk of incorrect usage of equipment.
✓ **Bulks formulation**

Materials including a table, a Microbial Active Sampling and Non-Viable Particles counter were exposed so that obstructing the outlet of air in grade B room used for formulation. Doors of the aseptic room are not of an adequate design since having handles, knobs and locks, presenting difficult to clean and disinfect surfaces within aseptic areas. Aluminium phosphate (GSK) container stored in the cold room was not bearing the sterile status in the label.

✓ **Quality control areas**

There were two cold storage areas in QC that appeared adequate for current needs. There was generally good separation of samples and materials; including stability and retention samples. It was indicated that 230 vials of each batch retained. Cold storage space had secured access. The map on one door indicated an allocated space for R/D material, though none was present at the time. Staff indicated that access controlled by QC supervisor was sufficient to prevent potential for mix up with R/D material but it was recommended that better physical segregation of this R/D space be introduced (e. g. zone demarcation; shelf labelling or caging).

✓ **Animal facilities**

The animal facilities were clean and well maintained. There were crawling and flying inspect controls at entrances. SPF animals are supplied from contracted suppliers. Each shipment of animals is supplied with certificates re-health status. Incoming animals are held in quarantine rooms for specified hold time before transfer to experimental rooms. Sentinel animals are maintained in mouse and guinea pig rooms. On a quarterly basis these are sent for analysis. Procedures are documented for responding to an identified pathogen in a sentinel animal. Environmental conditions in the animal facilities are consistent with WHO Manual for Quality Control of Diphtheria, Tetanus and Pertussis Vaccines. [20-24°C mice and guinea pigs; 40-60 RH; 100% fresh air with 20 changes per hour; 150-300 lux]. There were three rooms each for guinea pigs and mice. However, it was indicated that overlapping assays may take place in one room. The above referenced manual recommends avoidance of overlapping tests in one room. It was not possible to view the immunisation taking place during the inspection.

The reference wP vaccine is from the manufacturing subcontractor and the reference D and T are from EDQM. Janssen accept unitage assigned by supplier. Reference material was supplied yearly. These were stored in alarmed and calibrated storage facilities. Pertussis challenge strain was from the manufacturing subcontractor and stored in liquid nitrogen freezer. Sample fridge was well maintained with adequate storage. Trend analysis of reference ED₅₀₅ (using MiniTab statistics programme) was initiated in 2015. This is also a recommendation of the above referenced manual.

### 3.11 MATERIALS

The reception of material and packaging material was managed through implemented procedures.
3.12 DOCUMENTATION
An effective document management was in place. An electronic document management system was used and documents as batch record, used in aseptic area were also controlled by quality assurance. Archive room was secured with dedicated access and a list of personnel with access to the archive room was available. Document were stored in a dedicated cabinet and protected from fire by a special system waterproof. A logbook was available for the management of the archive documentation.

3.13 GOOD PRACTICES IN PRODUCTION

✓ Hepatitis B drug substance manufacturing
According to the common technical document in the part 3.2.S, the final sterilisation by filtration was performed just before the dispensing. Before this final sterilisation no bioburden is carried out.
The pre and post integrity test of the sterilising filters is performed after each sterile filtration process. The integrity of the sterilising filter is not performed after the sterilisation of the filter but performed before the steam sterilisation of the filter.

✓ Bulk formulation
The pre and post integrity test of the sterilising filters is performed after each sterile filtration process however, the pre-integrity test is performed before the steam sterilisation and not after and this was not documented and duly justified.

✓ Packaging operations
Vials for visual inspection were delivered by conveyor on line from the capping area. The first stage check was by an automated checker. This was indicated to be qualified via a Knapp test kit every year. The batch record indicates that every hour a small set of defect vials (clearly marked on cap) were processed through machine and record made as to whether these were correctly identified. The automated visual inspection machine was qualified yearly using a Knapp test set of vials. The requirement was for greater proportion of correctly identified rejects than manual reading. There was a high proportion (about one in six/seven) of a batch rejected by the automated machine and it was recognised that the vaccines inspected, containing whole cell pertussis and/or aluminium adjuvant, were challenging for machine inspection. All machine rejected vials were inspected manually. Manual inspectors sort rejected vials into critical, major and minor defects. At the end of the inspection, these were further sorted by defect type and results reported in the batch record. Annual trending of defect types was performed (though not reported in the PQR) and alert limits per defect type were set. It was indicated that a result exceeding a specification would trigger an investigation. However, there was no overall reject limit set for a batch. AQL checking of machine passed and manual inspection passed vials were performed by production staff (two inspectors check each set).

3.14 GOOD PRACTICES IN QUALITY CONTROL
Provisions were in place for the control and testing of starting materials and intermediate, bulk and finished products according to the established procedure with trained personnel. The test
specification, testing methods, equipment and facilities were considered adequate and suitable to the quality control activities as required.

✓ Sterility test
The validation report of the sterility test for Quinvaxem monodose and multidose was not provided in the data package submitted for the prequalification and for the licensing purpose. However, the company highlighted that these reports were available for review under request. The current sterility test for Quinvaxem vaccines (1D, 5D and 10D) was performed using direct inoculation on FTM media and incubation at both 20-25°C for 14 days and 30-35°C for 14 days. *Aspergillus brasiliensis* and the used in-house isolate do not show growth in the used FTM media.

According to the pharmacopoeial monograph, for products containing a mercurial preservative that cannot be tested by the membrane-filtration method, fluid thioglycollate medium incubated at 20-25 C may be used instead of soya-bean casein digest medium provided that it has been validated as described in growth promotion test. Accordingly, the company has initiated sterility test suitability studies and concluded the following:

In spite of due diligence efforts and exhausting feasible options, including high dilution and use of neutralizers, to inactivate the antimicrobial property of the preservatives in MDV, it can be concluded that the inability to recover the inoculated organism is attributable to the microbial or microbiostatic activity of preservatives in Quinvaxem MDV. So this finding, in combination with the low risk for product contamination with mold species during aseptic manufacturing, indicates that *Aspergillus brasiliensis* is not likely to survive or proliferate in undiluted and un-neutralized product QVMV, and may be considered technical justification for not including Aspergillus in the sterility test validation protocol for QVMV.

✓ Environmental Monitoring Program
Environmental monitoring was in place for all manufacturing areas including quality control areas. Airborne particles and MAS, settle plates, contact plates and personnel gowns and swabs for filling needles are considered for sampling. TSA media was used. Swab media containing lecithin and tween 80 were used as neutralizing agent.

The sampling location for the environmental monitoring were not based on risk assessment. Alert and action limits were implemented based on historical data.

In grade A areas, the alarms for non-viable particles of more than 5µm are >11 and >15 for alert and action limits respectively. The alarm setting was not considered adequate as consecutive low counts of particles of 5µm would not trigger.

2015 Q4 EM trend report for filling vials results were spot checked. It was recommended to improve the trend analysis regarding the type and reoccurrence of contamination. In order to improve the EMP Trend analysis and Alert/Action levels for viable in highly classified areas (A/B), frequency of positives should be considered for implementation, as recommended by USP 1116.

2015 Q4 EM trend report for drug substance, formulation and QC was spot checked.
✓ **Water monitoring program**

WFI, PW, pure steam and drinking water monitoring was in place. Specifications for WFI, PW and pure steam in place according to the EP. City water was tested every 6 months by external qualified company and internally quarterly.

WFI system was SIP every 6 months. TOC, conductivity and temperature were continuously monitored. PW system was sanitized over 85°C and ozonized every 3 months. The same WFI loop was used for HepBsAg and downstream processes. A risk assessment was performed and a mitigation plan regarding controlling the risk of cross-contamination was put in place. 2015 Q4 PW trend report and 2015 Q4 WFI trend report were spot checked.

✓ **Clean Compressed Air**

Air borne particles, water vapour, oil content, CO, and CO\textsubscript{2} contents and microbial count monitoring was in place. Specifications for Point of Use (POU) were in place. Monitoring results from January to September 2015 were spot checked.

✓ **Pure steam monitoring**

TOC, conductivity, microbial count, endotoxin, nitrate were monitored. The pure steam specification for bioburden was not more than 10 cfu/100 ml. Non-condensable gas, superheat and dryness were tested yearly. Monitoring results for 2015 were spot checked.

✓ **OOS**

Provisions for out of specification management was in place. OOS summary was included in the PQR. There was a clearly defined process for analysing OOS: Initially laboratory investigation. If no laboratory assigned error can be determined there was step up for production investigation. Invalidation of test through identification of error, does allow for retest. Individual test methods indicate any specific requirement about retesting. The default time for review of an OOS was thirty days, though this can be approved for an extension. Several OOS examples were spot checked.

✓ **Stability studies**

Provisions for On-going stability programme management were in place. At least one batch per year of finish product in every strength and every primary packaging type and one batch of drug substance (hepatitis B) were included in the stability programme. In certain situations, additional batches can be included in the on-going stability programme. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market were to be reported to the relevant competent authorities.

A report of the Quinvaxem stability study (single dose) relating to the move to production at the Incheon site was reviewed. Protocol indicated appropriate stability indicating parameters, consistent with those indicated in the submitted dossier for prequalification were assessed and that the three batches placed on test met specifications up to 36 months. The PQR contains reports of ongoing stability studies.
✓ **VVM and UN requirement**

VVM30 is used in Hepavax-Gene & Hepavax-Gene TF and VVM 14 is used in Quinvaxem (single dose and MDV). Labels were printed by external supplier, including variable data. VVM dots were affixed to the label rolls which were then placed back into freezer until use. During this stage of labelling absence of VVM placement can be checked and manually added if required. At affixing of label to vial, automatic check of variable data made and also check for absence of VVM (leading to rejection).

**PART 4: CONCLUSION**

Based on the areas inspected, the personnel 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, Janssen Vaccines Corp. (formerly, Berna Biotech Korea Corp) was considered to be operating at an acceptable level for compliance with WHO GMP guidelines.

All the non-conformances 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.