**WHO PUBLIC INSPECTION REPORT**  
**VACCINES MANUFACTURER**

### Part 1: General information

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>BB-NCIPD, Ltd., Bulgaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical address</td>
<td>Boulevard Yanko Sakazov No 26, 1504 Sofia, Bulgaria</td>
</tr>
</tbody>
</table>
| Contact person and email address | Mr. Sasho Ganov, General Manager BB-NCIPD Ltd.  
Tel: +359 2 944 61 91, Fax: +359 2 943 34 22, Cell: +359 893 308 640  
e-mail: bulbio@bulbio.com |
| Date of inspection    | 18 to 22 April 2016 |
| Type of inspection    | Routine |
| Dosage forms(s) included in the inspection | Injectable |
| WHO product numbers covered by the inspection | BCG (Lyophilized active component reconstituted with excipient diluent) Vaccine  
Difet (Diphtheria-Tetanus – Liquid form) Vaccine  
Tetadif (Diphtheria-Tetanus - reduced antigen content, Liquid form) Vaccine  
Tetatox (Tetanus Toxoid – Liquid form) Vaccine |
| Summary of the activities performed by the manufacturer | The facility has Production activities of medicines including BCG, Diphtheria-Tetanus and Tetanus Toxoid vaccines, nutrient media, diagnostic preparations. The manufacturing and quality control areas for bacterial vaccines production are situated on the third floor of the building; the animal house is on the fifth floor.  
The tests on animals are performed in the animal house on the fifth floor. The laboratories for QC are situated on the third floor and second floor (chemical analysis). The laboratory for production of crude tetanus toxoid takes place in completely separated closed areas, by means of separate equipment. |
PART 2: SUMMARY

General information about the company and site
BB-NCIPD Ltd. is a state owned firm registered in the Court of Sofia on 28 November 2000. The newly established firm fulfils the activities and takes the obligations of the former Production Department of the National Centre of Infectious and Parasitic Diseases. BB-NCIPD Ltd manufactures bacterial and viral vaccines, immunostimulators, blood proteins, antitoxic sera, nutrient media and diagnostic preparations.

BB-NCIPD Ltd. produces a wide range (more of 500) biological-products and preparations. These preparations are applied in the diagnosis, prophylaxis and treatment of the infectious diseases in Bulgaria. The company is sole provider of bacterial vaccines for the immunization programme of the Ministry of Health of Bulgaria.

BB-NCIPD Ltd. produces TETATOX, Tetanus vaccine, DIFTET, Diphtheria and Tetanus vaccine (adsorbed), DIFTETKOK, Diphtheria, Tetanus and Pertussis vaccine (adsorbed), TETADIF, Adsorbed Tetanus - Diphtheria toxoid; Td vaccine (with reduced dose of Diphtheria for adults), Antituberculosis BCG Vaccine for Intradermal Use, Freeze-dried and the Inactivated Vaccine against Crimean Haemorrhagic Fever (CHF).

The vaccines and other biological-products are exported in over 140 countries in the world.

BB-NCIPD Ltd. was prequalified by WHO supplier since 1991 for UNICEF and PAHO for the vaccines:
- TETATOX, Tetanus vaccine, WHO prequalified in 2006.
- DIFTET, Diphtheria and Tetanus vaccine (adsorbed), WHO prequalified in 2006.
- TETADIF Adsorbed Tetanus - Diphtheria toxoid; Td vaccine (with reduced dose of Diphtheria for adults), WHO prequalified in 2006.

Since 2002 the company has a certified system of quality management according to the standard ISO 9001:2000. This has been reviewed according to the standard ISO 9001:2008. The company has been inspected and certified as well for system of quality management applicable to the production of nutrient culture media, diagnostic sera and susceptibility discs according to the standard ISO 13485:2003.

History of WHO and/or regulatory agency inspections
The following inspections took place at BB-NCIPD Ltd.

<table>
<thead>
<tr>
<th>Date</th>
<th>Agency</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 January to 2nd February 2012</td>
<td>WHO audit</td>
<td>DT vaccine, Td vaccine, TT vaccine, BCG vaccine</td>
</tr>
<tr>
<td>9th to 13th July 2012</td>
<td>Bulgarian Drug Agency (BDA) GMP pre-certification inspection</td>
<td>DT vaccine, Td vaccine, TT vaccine, BCG vaccine, PPD Tuberculin Mammalian</td>
</tr>
<tr>
<td>4th to 6th July 2013</td>
<td>MFDS GMP inspection</td>
<td>PTT, PDT, IP</td>
</tr>
</tbody>
</table>
Focus of the inspection
The inspection focused on the production and control of BCG (Lyophilised active component reconstituted with excipient diluent), Diftet (Diphtheria-Tetanus liquid form), Tetadif (Diphtheria-Tetanus - reduced antigen content, liquid form) and the Tetatox (Tetanus Toxoid liquid form) Vaccines.

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
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control
PART 3: INSPECTION OUTCOME

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

Quality Risk Management
The procedure for Quality Risk Management was in place however. The company has provided the remedial corrective and preventive actions (CAPAs) adequately addressing the raised issues regarding the quality risk management.

Change Control
Provisions for change control were implemented according to the approved procedures. The major changes implemented by the company since last two years were presented as the following:

- Two new bio-fermenters with the working volume of 300L. One bio-fermenter was used to increase the capacity for cultivation of *Clostridium tetani* and the second was dedicated to the cultivation of *Bordetella pertussis*.
- New ink jet printer for coding of secondary packaging materials.
- New WFI generator.
- New clean area for B. pertussis cultivation.
- New warehouse for packaging materials.
- Renovation of warehouse for reagents.
- Construction and implementation of automatic system for clean rooms non-viable particles monitoring during operation in BCG manufacturing area.

The major changes planned for the coming two years were presented as the following:

- Introducing of inspection equipment with fully automatic control as a replacement of semi-automatic visual control – for vaccines filled in vials.
- Construction and implementation of automatic system for clean room non-viable particles monitoring during operation
  - filling of vaccines in vials
  - filling of diluent for BCG vaccine in ampoules
- Implementation of project for new filling line for diluent for BCG vaccine, approved by BDA.
- Implementation of project for reconstruction of rooms and building new clean area for new filling line for BCG vaccine, visual control, labeling and packaging, approved by BDA.
- Introducing a bar code labeling system.

The change control reports were spot checked.

Product quality reviews:
The annual product quality review was performed according to the implemented procedure. The PQR of Tetadif, Diftet, BCG and Tetatox vaccines manufactured in 2015 were spot checked.
The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the product quality reviews.

**Procedures for batch review and release:**
Procedures and steps for releasing medicinal products including vaccine have been spot checked. Responsibility indicated that the head of QA was responsible for the preparation of the summary protocol documentation and the head of QC was responsible on the release certificate of analysis (CoA) report. Samples were prepared along with the protocol documentation to be approved by the BDA for release of vaccines for the UN market.

### 3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general terms, resources were provided, including 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 generally defined and reviewed. Instructions and procedures were generally available. Qualification and validation of equipment, manufacturing processes and quality control testing methods were generally performed. Operators were instructed to carry out procedures, and records were made during manufacture. In general terms, key elements of GMP were considered however additional efforts were required to be in 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

Most of 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 was not allowed 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. However, the level of hygiene observed and the measures taken to maintain this were considered weak. The company has provided the remedial CAPAs adequately addressing the raised issues regarding the sanitisation and hygiene.

### 3.4 QUALIFICATION AND VALIDATION

Provisions for qualification and validation were in place. Qualification and validation reports were spot checked. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding validation of the processes and the qualification of the equipment.

### 3.5 COMPLAINTS and PRODUCT RECALLS

Complaints and records were handled according to the approved procedures. The procedures also include the requirement for destruction of recalled products which
may be implemented in case of any quality deviation and recalls. The QA official was responsible for receiving complaints. The SOP indicates the details including the contact numbers of the responsible person. Upon receiving of a complaint, the application form should be filled by the QA official. Recall of product with risk to the patients (domestic and international) procedures have also been covered by this SOP. There was 3 days timeframe to respond to the recalls which was part of the QA and QC heads’ responsibility. The destruction procedures of recalled products with quality deviation were mandated by the Regulation no. 28, Bulgarian Ministry of Health. The Manufacturer claims that there was no complaint reported to the quality of any vaccine since 2012.

**Adverse event following immunisation**
Procedures on AEFI (Medical department/drug safety) have been followed by the medical department of the BB-NCIPD. This department was responsible the post market of all pharmaceutical products including vaccine. Only 2 cases of adverse events reported in 2014 and received from BDA in 2015 with Tetadif vaccine. Two side effects abscess and oedema at the site of injection were reported. These cases were received from the BDA. No adverse event was received for the year 2015 for vaccines.

### 3.7 CONTRACT PRODUCTION AND ANALYSIS

This section has not been reviewed however, the manufacturer claims that there was no external contactor to perform testing, service and calibration.

### 3.8 SELF INSPECTION AND QUALITY AUDIT

**Self-inspection**
Provisions of self-inspection were in place according to the approved procedure. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the self-inspection.

**Supplier’s audits and approval**
Supplier qualification was spot checked. The procedure regarding the Supplier Qualification in force indicated 3 categories of suppliers: A for regular supplier including suppliers of primary and secondary packaging components and these suppliers were audited every 2 years, B for suppliers used from time to time and C for potential suppliers. There was a provision in place for annual evaluation and regular audits of the suppliers.

### 3.9 PERSONNEL

BB-NCIPD Ltd. was staffed with qualified personnel including physicians, pharmacists, biologists, chemists, economists and supporting personnel. The total number of employees was around 396. Of 253 for production, 61 for QC and QA, 19 for storage and distribution, 23 for administrative and financial activities, 15 for technical services and garage, 20 for housekeeping and security guards and 5 for medical department.
The breakdown of the personnel in the manufacturing of active ingredients for bacterial vaccines was 6 for “Diphtheria” Unit, 6 for “Pertussis” Unit, 14 for “Concentration and purification of tetanus toxoid” Unit and 9 for “Crude tetanus toxoid” Unit.

49 employees work in the manufacturing of BCG vaccine among them 14 were graduated from university, 15 have finished specialized secondary schools (colleges) and 20 have finished ordinary secondary or other schools.

80 employees work in the manufacturing of final products in amps/vials, visual inspection, labelling and packaging of bacterial vaccines. 21 were graduated from university, 33 have finished specialized secondary schools (colleges) and 26 have finished ordinary secondary or other schools.

Training:
Training record for personnel was spot checked. The personnel were trained according to the approved training procedures as well as to the on job specific procedure.

The training and qualification for the visual inspection operators was checked and considered satisfactory and appropriately organized.

Job description:
Jobs descriptions were in place. The job description record for the Microbiology personnel in QC lab has been spot checked.

Personal Hygiene:
Procedures governing the healthy conditions of the personnel were in place describing the health requirement for personnel employed in the BB-NCIPD. The employee should be free form tuberculosis, chronic disease and skin lesions etc. The annual health examinations for all employees were in place which includes blood and urine tests, cardio, chest and visual examination. Visual inspectors were examined every 6 months. Monteux test was also included. The head of the unit was responsible to examine for daily hygienic condition of personnel. Personnel were aware to report to the head unit if there was any health condition.

The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the personnel.

3.10 PREMISES and EQUIPMENT
The manufacturing and quality control areas for bacterial vaccines production were located on the third floor of the building; the animal house was on the fifth floor. The manufacturing units involved in the production were:
- tetanus toxoid unit
- diphtheria toxoid unit
- inactivated B. pertussis suspension unit

The production of crude tetanus toxoid takes place in dedicated areas, by means of separate equipment. The cultivation of C. diphtheria and B. pertussis were performed in dedicated facilities as well.
The access of unauthorized personnel not permitted. Procedures for disinfections of equipment and instruments used during the production were carried out in the manufacturing areas.

No cultures of microorganisms other than strains of *Cl. tetani*, *C. Diphtheria* and *B. pertussis* approved by the BDA for vaccine production were introduced into the dedicated manufacturing areas. Cultures and vaccines were protected from the daylight and ultraviolet light at all stages of manufacture, testing and storage.

The description of the rooms for manufacture of active ingredients and bulks, for formulation of the final bulk, filling and sealing, visual inspection, labelling and packaging of bacterial vaccines TT, DT, Td in vials were provided in the site master file.

The manufacturing areas for BCG vaccine were located on the first and second floor of the building. The manufacturing areas for diluent manufacturing were located on the first, second and third floor of the building.

The manufacturing units involved in the production of BCG vaccine were:

- BCG laboratory
- Filling and sealing laboratory (for filling of diluent in ampoules)
- Rooms for preparation of intermediates, cultivation, formulation of the final bulk,
- filling, freeze-drying and sealing of BCG vaccine.
- Rooms for diluent preparation and sterile filtration.
- Rooms of visual inspection, labelling and packaging of BCG vaccine.
- Rooms of visual inspection, labelling and packaging of diluent.

The description of the rooms for manufacture of BCG vaccine and its diluent were provided in the site master file. The drawing for classified areas were to be corrected and improved to reflect the real applied classification.

**Visual inspection, Labelling and packaging**

This chapter was covered for the BCG vaccine. During the tour the visual inspection was observed. Visual inspection is done by 7 visual inspectors with 6 performing inspections in cabinets with white and black background and the 7th visual inspector for backup, supervise and support. The ampoules found conform were transferred from plastic trays to metallic trays and the non-conform ampoules were collected separately.

The total number of conform ampoules post visual inspection transferred to labelling was not counted. The number of ampoules conform to visual inspection was obtained from the total number of inspected ampoules subtracted by the number of rejected ampoules. It was suggested to the company to organise the workflow and instructions for visual inspection and labelling in order to have an adequate reconciliation system in place.

The pre-printed labels and VVM were stored in closed areas. The VVM 30 was stored at -25 to -45°C freezer equipped with visual temperature monitor which was also connected to a central monitoring system.

The qualification of visual inspectors was performed in accordance with the
implemented procedure using a set of 200 ampoules with 190 correct ampoules and 10 with defects including 1 empty, 1 broken, 3 with impurities of glass particles, 4 cosmetic defects and 1 with a sticky powder. The qualification required no false results and the process were considered satisfactory since some defects were not detected by an unexperienced visual inspector. Visual inspectors were allowed to take rest for 15 minutes after 45 minutes inspection session.

Procedures to contain BCG ampoule breakages that might be happening during visual inspection were in place.

**Storage areas:**
Storage areas were well designed and clean with good shelving conditions and proper separation and segregation zone of quarantined products. The temperature monitoring systems were in place.

**Water system**
WFI was produced through two stills from treated city water. Capacity: 300L/H. 4 tanks were available for WFI storage. Between 4 to 5 tons needed for daily operations.

The WFI loop was equipped with 35 user points.

The validation of water system was performed according to WHO TRS 970 annex 2. This validation started in July 2015 after the installation of the TOC testing devices on each return loop. R2A media was used for bioburden testing according to the European pharmacopoeia. TOC and temperature were continuously monitored.

Phase one and two during two weeks with sampling of all user points daily. All results conform to the specifications. Phase three (sampling once a week of all points) up to 16th week results were presented.

**Quality control areas**
The microbiology laboratory has been divided into 3 parts. The main part was considered as unclassified room which was adjacent to two segregated chambers (chamber 1 and 2). Each chamber consists of one laminar flow class A with background class B. The 1st chamber was designated mainly for testing of live BCG Growth test (BCG particles number). The 2nd chamber was used for sterility tests of final product containers.

**Quality Control Chemistry laboratories:**
Reagent containers were labelled appropriately. Qualification/calibration of pipettes, equipment was in place. Procedures for disposing of chemical waste have been spot checked.

**Quality Control Biological laboratories:**
Samples receipts and results reporting were manually entered. Laboratory Information Management System (LIMS) or an equivalent software system was not available for samples receipt and test results reporting/documentation. Procedures for out of specification and/or re-test were in place. The instructions were indicated in the SOPs of each specific test method.
Results of Tetatox vaccine 10 ml (20 doses) has been spot checked. The vaccines samples were tested for visual appearance, sterility, extractable volume and abnormal toxicity. All test results found to be within the specifications. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the quality control activities.

3.11 MATERIALS
In general terms, the arrangements for the handing of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage were in place. Arrangements for the handling and procedures for destruction of rejected materials and products were in place as well. Sampling of incoming chemicals and primary packaging materials was implemented according to the approved procedure. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the material management.

3.12 DOCUMENTATION
This section was not inspected in details although the arrangements for the preparation of documents were in place.

3.13 GOOD PRACTICES IN PRODUCTION

Pertussis Manufacturing
The design of the process was considered deficient in that the inactivated intermediate was processed in the contained area where live pertussis was handled. At the end of the thermal inactivation of the B. pertussis, the dispensing of the inactivated pertussis intermediate takes place in a room with negative pressure within the laminar air flow where live pertussis was processed. The company has provided the remedial CAPAs adequately addressing the raised issues regarding the risk of cross contamination between live and inactivated material of B. pertussis. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the good manufacturing practices for pertussis manufacturing.

Tetanus Toxoid Manufacturing
The flow of contaminated wastes from the unclassified room in Tetanus manufacturing site located 3rd floor through the pass-box connected to room (sample collecting) which of class A/B and then through pass-box connected to incubator room of class D and through room 10 (Bioreactor room) of class B then terminated in the 2-doors autoclave which was located in the solution preparation room 4 (room class D). The method of disposing of potentially contaminated waste was in place in accordance with the procedures: movement of crude Tetanus Toxoid for concentration and purification.

Environmental monitoring
Filling room of liquids: only one NVP counter was used for EM at 4 locations in grade A and one in grade B at capping station and one in the room of grade B. The viable active air sampling was done 30 min before the end of the filling process at the location near the needles. No other sampling points were considered within grade B
areas. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the environmental monitoring.

**Formulation**

Formulation room for liquid vaccines:
The mixing tank was CIP and SIP in a room claimed as of grade A, moved to grade A, weight calibrated, and the start of the formulation by adding aluminium hydroxide and actives according to the formulation formulae, homogenisation, sampling for QC testing and retain samples. The connections from the formulation vessel to the filling pump take place under grade A. The transfer was done by a vacuum pressure pump where the air pass through a vent filter to the solution to be push to the filling line. The filter was sterilised with the sterilisation in place (SIP) cycle of the vessel however; the integrity test was not considered. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the formulation process.

**Formulation and filling line for Diftet, Tetadif and Tetatox**

Filling room 14fp: this filling machine was dedicated to the filling of vials. The filling machine was equipped for sealing of ampoules as well. It was recommended to dismantle these parts of sealing as these were no more used and presenting additional risk to the filling process. Depyrogenated vials were manually moved from the cooling station of the tunnel to the filling machine. The filling machine was segregated with simple restricted barriers. The doors of the barriers open into grade B. The filling line has 4 filling needles. The filling and stoppering take place within grade A and the capping take place within grade B. The grade A air supply was not provided for the capping station and for the transfer of uncapped vials from the filling line to the capping station. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the formulation and filling process.

**Formulation and filling for BCG vaccines:**
The BCG vaccine was manufactured in the dedicated area entitled Laboratory “BCG vaccine” including rooms for preparation and sterile filtration of diluent. The formulation of the final bulk (preparation of vaccinal suspensions) takes place in a room of grade B with Laminar Air Flow of grade A. The sampling probe in the Laminar Air Flow was not positioned vertically.

The aseptic filling of the BCG takes place within a restricted access barrier system with Laminar Air Flow of grade A surrounded with grade B background. The ampoules were placed in covered metal cases. The ampoules were sterilised in the double door autoclave and depyrogenated in the ovens in a room of grade B. The ampoules were manually loaded in a trolley cabinet provided by air of grade A from the top (vertically). The ampoules were transferred to the filling rooms and manually transferred to the filling line under grade A. After filling, the ampoules were manually transferred in the cases to the freezers (at -35°C). The frozen ampoules were manually transferred to the lyophilizer. The loading and unloading of the lyophilizer was manual. After the unloading of the lyophilizer, the ampoules were moved to the sealing room. Ampoules were manually and individually placed on a metal holder.
fitted with 75 holes for ampoules placing. Two holders (150) were placed in the sealing machine to be sealed under vacuum. The batch size of the BCG vaccine was around 16,000 ampoules. The sealing process last around 13 hours.

Biomedical freezers were installed in a room to freeze the BCG in ampoules before transfer to the freeze drier. The circulating fan of the freezers sucks in cold air that has been circulating in the chamber and sends it out for further circulation after recooling. According to the company procedures, the two freezers were switched off during the media fill test (MFT). The environmental monitoring was not considering sampling locations close to these freezers as control measure to the risk of contamination.

The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the formulation and filling processes.

**Sterile filtration and bioburden**

The sterile filtration at the end of the diphtheria and tetanus toxoids purification processes were considered weak.

The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the sterile filtration process.

**Media Fill Simulation**

The BCG filling, freeze-drying and sealing process was a risky process due to manual interventions of open ampoules since the exit from the autoclave to the sealing machine. The aseptic process simulations (APS) should be as close as possible to the routine process. The freezers were switched off during the MFT. The commercial batch size was indeed around 16,000 ampoules. The formulation was not considered for media simulation.

One half of the ampoules filled were incubated at 20-25°C during 7 days followed by incubation at 30-35°C for another 7 days period and the reverse was done for the other half. The PIC/S recommendation is that all filled containers should be incubated first at 20-25°C during at least 7 days and then after a possible first reading incubated at 30-35°C for another 7 days period. It was documented that some strains of moulds coming from the environment were not able to grow any more after a first incubation period of few days at 32.5°C.

The APS for the liquid vaccines filling line was reviewed for the 5 ml filling volume and showed weaknesses. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the media fill simulation.

### 3.14 GOOD PRACTICES IN QUALITY CONTROL

Procedures and specifications were in place for the control of starting materials, intermediate, bulk and finished products.

Media used for testing and environmental monitoring were in house prepared. Contact plates contain lecithin and Tween 80 as neutralizers however the glutaraldehyde used as disinfectant cannot be neutralized with these components and the experimental study reviewed did not follow a standardized protocol to assess this point. The environmental monitoring programmes showed weaknesses that the company has adequately addressed through the remedial corrective and preventive actions.
Out of Specification
Provision for Out of Specification (OOS) handling was spot checked and showed weaknesses.
The company has provided the remedial CAPAs adequately addressing the raised issues regarding the out of specification handling.

Stability program plan
Stability program plan for BCG lots during 2016 has been provided for review which includes the long term stability, thermal stability and total bacterial count as well as tests required as per release specification of final product.
Stability plan for adsorbed [Tetatox, Difetetkok, Diftet and Tetadif] vaccines was in place. It covers the long term stability, accelerated and the test of 3 consecutive batches in case of change equipment i.e. from production plan.
Stability program plan for DTP components has been reviewed for long term stability. One vial from each vaccine component and one vial from each presentation are tested.

Analytical methods validations
Procedures for analytical method validation has been reviewed which follows the WHO and ICH requirements. The validation of total bacterial count of BCG has been reviewed. The validation assays performed once a year according to the implemented procedure. Three assays performed in 3 different consecutive days by different operators using a spectrophotometer machine. Forty ampoules were used per day per assay. Results prepared and hand calculated by one operator and calculation confirmed by a second operator.

Batch record review of Tetadif and BCG vaccines:
A batch record for Tetadif and the corresponding toxin and toxoid batches as well as a batch record of BCG vaccines were spot checked and gave rise to weaknesses. The company has provided the remedial corrective and preventive actions adequately addressing the raised issues regarding the batch record review.

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, BB-NCIPD, Ltd. 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 inspection 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.